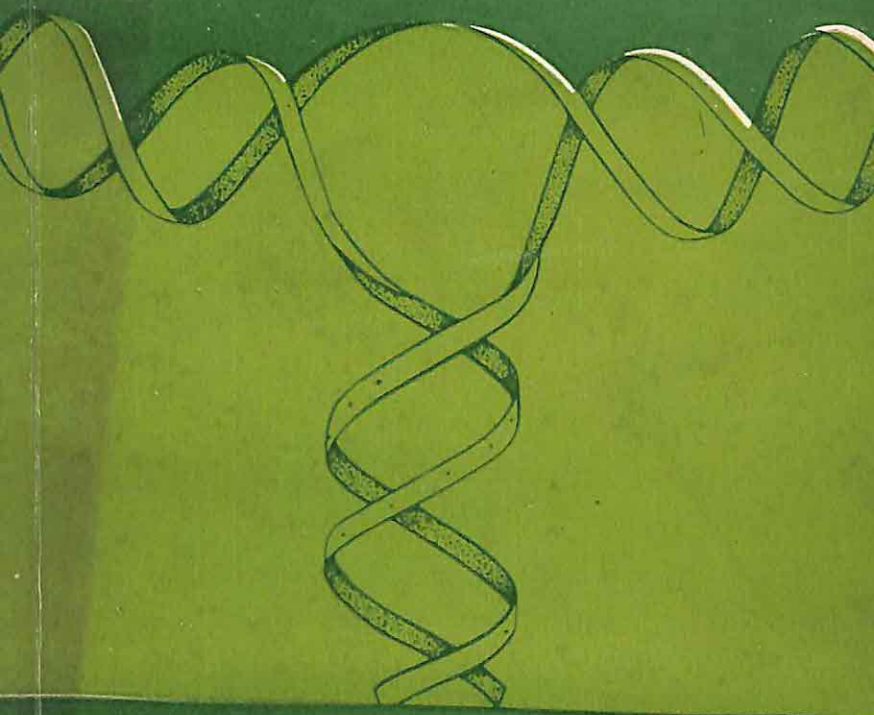
FRONTIERS OF

Life Sciences



JAGJIT SINGH

Dr Jagjit Singh is, perhaps, the most prolific author of science popularization articles and books in India. He has regularly contributed articles in all areas of science to several distinguished newspapers and magazines such as *The Hindustan Times*, *The Times of India*, *The Illustrated Weekly of India*, *Science Reporter* and *Science Today*. He has also authored a large number of books including *The World of Science and Technology in 2000 A.D.* (1979), *Modern Cosmology* (1971), and *Great Ideas in Information Theory, Language and Cybernetics* (1965). For his outstanding contributions he was honoured with the Kalinga Prize for science popularization by UNESCO in 1963. Other recipients of this prestigious award include such celebrities as Bertrand Russel, George Gamow and Louis de Broglie.

To
KHUSHWANT
who called the piper to play the tune

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Life Sciences

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Preface

The essays in science popularization collected here were written in response to a telephone call in October 1979 from Khushwant Singh when he heard the news of the award of Noble Prize to Abdus Salam. He called me to write for his fortnightly magazine, *New Delhi*, a 'popular' exegesis of Salam's work that had won him the Prize. It would be presumptuous on my part to suppose that this single piece made his readers instantly crave for 'more of the same'. But the fact remains that immediately thereafter he commissioned me to write for his magazine a regular column titled 'Scienscope'. My brief was to describe in simple rather than technical terms intelligible to the interested layman the work on the frontiers of science with the rider that every effort must also be made to preserve the precision and accuracy of the work reported.

A few months later when he shifted to *The Hindustan Times* as the editor, he made me switch my column to its Sunday edition.

Most of the essays in this collection were first published in *The Hindustan Times* though a few appeared in *New Delhi* and elsewhere. I hope the collection of these scattered pieces in one place will help disseminate scientific temper in our midst especially among the intelligent citizens. If it also promotes greater awareness of some of the latest developments in science among the elite—administrators, statesmen, students and even scientists

anxious to acquaint themselves with disciplines other than their own, my purpose in writing and collecting them will be doubly served.

February 1984 JAGJIT SINGH

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Science Popularization : My Experience 1

In 1949 when I was in London on a year's study leave I was greatly captivated by the science popularization articles J.B.S. Haldane used to publish every week in the *Daily Worker*. In these articles he almost always managed to perform an amazing act of creativity—what Koestler later called bisociation—by tying together a whole gamut of subjects from biology and aeronautics to social polity and engineering in a single Ariadne's thread. On my return back home in 1950 I resolved to imitate the inimitable Haldane. I began by offering Chalapati Rau, the then Editor of *National Herald* in Lucknow, a science popularization article every Sunday in his paper's magazine section. The encouragement I received in response to this initial effort spurred me to continue the work with renewed vigour.

After nearly thirty year's practice I am now fully convinced that every civilized or industrialized society needs science popularization almost as much as science creation. This is because of the novel developments in science that began to occur around the turn of the century, which resulted in its exponential growth and the consequential absurd fragmentation on the one hand, and its prolific industrialization on the other. One consequence of these developments is increasing mystification of modern

science, which raises the question as to why its core must be simplified to make it comprehensible to the enlightened layman.

There are three prime reasons for demystification or popularization of modern science. First, it is required to promote scientific temper in the community. Second, it is necessary for the education of our public administrators. Third, it is an essential counter to the continual fragmentation of science.

Take first the promotion of scientific temper. While it is not easy to define precisely the ingredients of scientific temper, there is no doubt that its widespread diffusion in our midst is a necessary prelude to overcoming what J.B.S. Haldane once called our 'culture lag'. Our culture lag is that unhealthy telescoping of the habits of thought appropriate to the Vedic age with the practice of jet age that is at the root of our inveterate habit of doublethink—the amazing power of even otherwise highly intelligent men to harbour such incompatible mixes as Marxism and Vedant or engineering and astrology without any apparent intellectual qualm or embarrassment. It is the outcome of a conflict between the basic drives of a peasant economy trying to leap the technology gap on the one hand, and its obsolete ideological or cultural system that still believes that the world around us is all a veil of *maya* or illusion that ought to be renounced rather than remoulded. This attitude of mind, by emphasizing the transitoriness and vanity of personal life, distracts attention from all immediate surroundings and thereby tends to arrest the desire for material improvement, which is often the incentive leading to an advance in practical scientific knowledge.

Consider next the education of our public administrators. Everyone agrees that proper orientation of our public administrators towards science and technology is a

'must' in a technologically developing society like ours, for the interactions of science and society operate to a very great extent through the public administrator. He is the channel through which scientists and technologists modify society and through which they are themselves modified by the society. He can promote traffic between the two cultures or he can block it. That is why he can be either a pump that keeps the stream of ideas and schemes going, or a sink wherein the stream coagulates, making the coagulated mass stink.

Now it is certainly not knowledge in depth of any particular field of science and technology, let alone all fields of science, that he requires to enable him to function as a pump. The sheer bulk of scientific knowledge, which even a specialist in his own field of endeavour must carry, is frightening. And it is growing exponentially every day. Therefore, in educating administrators, we cannot possibly require them to acquire such knowledge in depth. There is neither time nor cerebral capacity to imbibe such a volume of scientific knowledge. All that can reasonably be done is a policy of appeasement, offering a side dish of scientific salad to the humanist and its humanist analogue to the scientist in the hope that it will enable him to use other men's minds. For clearly, whatever his own expertise, the secretary of a technical ministry such as that of Petroleum, Chemicals and Fertilizers, or Steel and Mines, will still have to make decisions in matters of which he may know nothing at all. It is to the mastery of this art—the administration of the unknown and unforeseen—that his education should be directed. It is to put it simply, the art of using the knowledge of whole groups of experts often working at cross purposes to make decisions for the benefit of society. The problem of using the expertise of others in decision making, the prime task of the public

administrator, is difficult but not insoluble. Its solution lies in the public administrator acquiring an *understanding* of the core concepts of some major branches of modern science and technology rather than skills in manipulating their techniques. It is possible to present their core to the educated layman in a brief compass in such a way as to enable him to begin a dialogue with the expert in a meaningful way.

Last but not the least is the present inevitable tendency of science to fragment into increasingly narrower disciplines. The time seems to have come when this tendency should be consciously countered by parallel efforts to evolve an overall and integrated perspective of the diverse branches of modern science. That is, we must also underscore, however briefly, the essential interdependence of scientific fields and break down their growing parochialism. A bridging mechanism must be devised to link thought and experiences originating from diverse starting points and premises. Such a bridging mechanism is science popularization. It automatically provides opportunities for challenge and cross-fertilization, both being essential counterweights to elitism and arrogance in science. It also emphasizes the central unity of science in our affairs and thereby helps discover its direction and meaning for the human condition. In the absence of such a bridging mechanism, science is liable to degenerate into an incommunicable chaos of a miscellany of disciplines and subdisciplines, comprehensible only to an ever-diminishing circle of fellow experts.

I am aware that there is a school of scientists who believe that modern scientific theories will remain an incomprehensible mystery to the layman and nothing can be done about it. They do so because scientific advances nowadays often give rise to new concepts such as 'colour',

'charm', 'beauty' and 'strangeness' in particle physics that are either inexpressible in ordinary language or at best appear too queer to be credible. But ordinary language is not a finished thing. It continually grows and generates of *itself* increasing power to express new ideas that were earlier beyond its reach, exactly as modern science and technology do. Unfortunately, the growth of the vocabulary of our daily language has lately not kept pace with our burgeoning science and technology. It is these uneven growths of ordinary language and science and technology that makes science communication the problem it is. There is simply not enough time for the new vocabulary of science to gain wide currency. As a result a science popularization piece intended to explain to the layman a new discovery or development in science must build up from scratch the basic vocabulary of the field if it is to be intelligble to him. This is why any lay exegesis of a new scientific development cannot be both concise and intelligible. If it is concise it will not be intelligible, and vice versa. This problem of making science communication both concise and intelligible is immensely compounded if the audience aimed at includes a significant proportion of people who, like the two Toynbees, father and son, or our own Khushwant Singh, feel terribly deprived and alienated in a technological society because of their exclusive preoccupation in early life with humanities at the expense of science. The basic problem of science communication then is how to make presentations that reconcile the contrary requirements of conciseness and intelligibility to an audience that includes a significant fraction of people like Toynbees and Khushwant Singhs. Like Pontius Pilate I simply pose the question and depart without waiting for the answer.

Life, Our Biological Heritage : Its Genesis 2

The genesis of life, our biological heritage, is a primeval mystery. The earlier ages had, no doubt, their theories. But their authors, totally ignorant of the complexities of the phenomenon of life, had naive ideas as to how life actually arose on earth. As usual, the greater the ignorance the more pompous the verbiage devised to mask it. *Generatio acquivoca, generatio primaria* expressed the belief that fully formed organisms arise miraculously out of non-living matter. Even as recently as the turn of the century the celebrated biologist, J.H. Woodger, could do no better than define life in a question-begging way as 'an X in addition to carbon, hydrogen, oxygen, nitrogen, etc. plus organizing relations'. Perhaps the mysterious X-component was thrown in to provide a foothold for some sort of mysterious spirit which could either be equated to a soul after the forthright fashion of medieval theologians such as St. Thomas Aquinas, or to a more devious, if less tangible, *élan vital* of the vitalists and creative evolutionists such as Henry Bergson and Lloyd Morgan.

Modern science has now put an end to all this mystical rodomontade of the creative evolutionists and their allies, the vitalists and telefinalists. It is now realized that the phenomenon of life is almost impossible to define. No

matter which definition you adopt, whether physiological, metabolic, biochemical, genetic, thermodynamic or whatever, you can always find counter examples to falsify it. The refusal of life to fit into a neat definition of our making is merely a reflection of its manifold complexity. It is, therefore, no wonder that the origin of life is a question which science was not ripe enough to handle till almost now. This is why Charles Darwin, the father of biological evolution, frankly admitted: 'It is mere rubbish thinking at present of the origin of life; one might as well think of the origin of matter'.

During the century or so that has elapsed since Darwin made this remark, scientists have indeed formulated theories of the origin of matter as well. As might be expected, the two problems—the origin of matter and life—are, in fact, curiously connected. But the connection will be more obvious if I first recall Darwin's own contribution to the evolution of life.

As is well known, he was the first to show in a convincing manner that life had not arisen by special creation of each species but by slow descent from very different ones in the past, some of which have left their vestigial remains in fossils buried under the rocks. The pre-Cambrian rocks, the oldest group in which fossils have been found, are evidence of an abundant and varied life as long as 500 million years ago. Fossils of many thousands of different kinds of Cambrian animals unearthed by students of extinct organisms, show that the shallow sea of the times must have teamed with prolific life. Considering that all the phyla and many classes of animals represented in the Cambrian fauna had advanced far along the evolutionary line despite their primitiveness, it seems that at least three-quarters of animal evolution must have occurred before the onset of Cambrian times

500 million years ago. Consequently plants and animals must have in all probability lived in the earth's oceans for at least 1500 million years before the Cambrian period, even though all the pre-Cambrian animals and plants except the calcareous algae, lacking hard parts, have left no satisfactory record of their former existence.

It is this problem of the genesis of pre-Cambrian forms of life that is curiously connected with theories of the origin of matter which Darwin with remarkable prescience divined but dodged over a century ago. Recent advances in cosmology have now produced convincing evidence to show that thermonuclear reactions and subsequent explosions in the interiors of stars, generate all the chemical elements more massive than hydrogen and helium, and then distribute them into the interstellar medium from which subsequent generations of stars and planets form. There are thus two kinds of stars in our universe. First, there are the older population II stars formed out of primeval hydrogen formed soon after the first burst of explosion of the giant primeval atom which gave birth to our expanding universe some 10 billion years ago. Second, there are the younger population I stars formed out of the cosmic material enriched with heavier atoms spewed out by the older population II stars. Our own sun is a second generation population I star, which is believed to have condensed out of a self-gravitating nebula of cosmic material about five billion years ago. If we compare the composition of life with the average composition of this cosmic material of the solar nebula and the average composition of our earth now, we find a remarkable coincidence as suggestive as the coincidence of the salt content of blood and of the primeval seas. We observe that the composition of life is intermediate between the average cosmic and terrestrial compositions. Ninety nine per cent

of material of both the cosmos and of life is made up of six atoms, namely, hydrogen, helium, carbon, nitrogen, oxygen and neon. Can it be that pre-Cambrian life on earth originated when the chemical composition of the earth was much closer to the average cosmic composition and subsequent events have changed the gross chemical composition of the earth? The compositions of outer planets such as Jupiter, Saturn, etc. are much closer to cosmic composition than the earth. They are largely gaseous, with atmospheres composed principally of hydrogen and helium, but also laden with methane and ammonia in smaller quantities, besides traces of neon and water. This circumstance very strongly suggests that the outer planets were formed out of material of typical cosmic composition. Their very large masses and great distances from the sun have made impossible the escape of lighter elements such as hydrogen and helium from their atmospheres, which our much less massive and much more warm earth could not retain very long after its formation.

What precisely the composition of this primeval atmosphere of the earth was, is still uncertain, so that the nature of the photochemical reactions that preceded the emergence of pre-Cambrian life from inanimate matter cannot be correctly surmised. But it is now generally accepted that shortly after its formation, the earth's primordial atmosphere was very different from what it is now. Thus there is no doubt that there was no oxygen in the earth's original atmosphere as was pointed out by J.B.S. Haldane over fifty years ago. Presence of oxygen in any significant quantities would have led to the formation of an ozone screen absorbing all ultraviolet radiation of the sun. Such a screen would have greatly diminished the diversity of possible photochemical reactions on the

primitive earth. Attempts have been made to guess more precisely the composition of earth's original atmosphere by computer simulations of its likely evolution. Scores of computer runs with different initial conditions indicate that the current state of earth's atmosphere, surface and climate, can be explained in detail through the past interplay of known processes such as degassing from the earth's interior, ocean formation, dissociation and reactions of atmospheric gases, the greenhouse effect, etc. without invoking any extraordinary events. The run which has produced so far the best fit to contemporary earth seems to suggest that earth's early atmosphere consisted largely of water vapour, carbon dioxide, methane, and ammonia, not very unlike those of outer planets.

Biochemists have subjected mixtures of such gases, the putative components of earth's primeval atmosphere, to electric discharges (to simulate lightning flashes) and ultraviolet irradiation (to simulate primeval sunlight). By recourse to such simulations they have been able to produce almost all the essential building blocks of life such as amino acids and their long chain polymers usually called proteins* which are the solid core of living substances. It thus appears reasonable that all the essential life-forming material such as base adenine, pentose sugar, ribose, the lipids, etc. may have been produced in some fair concentration on the primitive earth. The simulated production of such material is, of course, relevant to the origin of life, but it does not suffice to explain how life arose out of inanimate matter.

What is required here is something that is a self-replicating, mutable molecular system, capable of interacting with its environment. Cells of contemporary life are

*The name proteins is derived from the Greek word *Proteios* meaning 'holding first place' in life processes.

such systems. They reproduce themselves by interaction with their environment. In such cells the nucleic acids, the stuff of heredity or what is now a household word called DNA, are the sites of self-replication and mutation. Laboratory experiments do seem to show how such self-replicating polynucleotides could have arisen. It is true that many of these laboratory experiments yielding materials of contemporary life such as proteins and polynucleotides, have been criticised on the ground that they do not in some cases simulate very faithfully the conditions prevailing on the primitive earth. But the criticism is only a small change in the riddle of life. The main difficulty in divining it now is the fact that polynucleotides, though self-replicating, have no catalytic properties, and proteins, though autocatalytic, have no reproductive process. It is only the partnership of the two molecules that makes contemporary life on earth possible. Accordingly a critical and unsolved problem in the origin of life is the first functional relation between these two molecules, or equivalently, the origin of the genetic code. It is this problem of producing a molecule of life, combining both the functions of catalysis and self-replication, under simulated conditions of primeval earth of some three to four billion years ago, that is currently occupying many microbiologists. The stakes are high because once such an autocatalytic and self-replicating molecule of life is produced, the way is then clear for its subsequent evolution into higher forms of life. For such an Adam molecule at birth will find itself literally in a molecular garden of Eden, where all the building blocks that present-day organisms must work hard at synthesizing, were available to it free. It would thus multiply pretty fast—even though without an Eve—until the accumulated supply of one of the intermediate components, say A, was

exhausted—a molecular analogue of Malthusian pressure of population on the means of subsistence. A premium would then be put on a variant able to catalyse the formation of the exhausted component A from a protein precursor B still present in abundance, thereby foreshadowing evolution by mutation and natural selection; and so on till a stage would arrive when selection would favour molecules capable of devouring others, that is, breaking them down to reorganize their constitution according to the devourer's own pattern. Such molecules were the precursors of future predators. This is how biological evolution seems to have conjured life out of its inanimate slumber. Having done so, it then piloted life all the way from its lowly origin as an autocatalytic and self-replicating particle of life to its present culmination in man as an increasingly complex crescendo of self-sustained patterns of chemical reactions.

Life, Our Biological Heritage : Its Unity 3

The basic unity of life is expressed in the so-called central dogma of modern biology. It is the belief that whatever happens in a bacterium will happen in an elephant. The reason is that the genetic code responsible for the reproduction of a bacterium is basically the same as that for the reproduction of an elephant, or any other animal or plant. The genetic code, which scientists are just about beginning to decipher, is the chief expression of the fundamental identity of all *terrestrial* life.

I have deliberately used the adjective *terrestrial* in the preceding sentence to emphasise the fact that there may well be other extraterrestrial forms of life differing from our own in some aspects. For while there are, no doubt, certain features of living systems necessarily common to them all, no matter where they arise, there are some others which are only contingent. The former are the outcome of the basic laws of chemical valence which are universally valid. Living matter, wherever it may occur in the universe, presumably requires a vast variety of complex compounds from which to synthesize itself. Carbon alone among the elements of the periodic table seems qualified to do so and thus serves as its backbone. The possibility that living organisms made of sterner stuff, such as silicon in lieu of carbon, may be

around somewhere in other extraterrestrial worlds has been suggested. But a silicon cell is not even a plausible 'perhaps' so far as we can tell at present.

The contingent features of life, on the other hand, are merely the result of evolutionary accident so that somewhere else, say, in the planetary systems of other stars of the Milky Way, or for that matter, on our own earth, a different sequence of events might have led to different characteristics. Thus it seems a mere chance that our own basic stuff of life, the protein, is made up of one form of amino acids rather than the other, for every one of the twenty odd amino acids of which proteins are made can exist in two isomeric forms. These two forms, L (levo) and D (dextro) are identical with one another except for the arrangement in space of the four groups attached to the basic carbon atom (see Fig. 1). As will be observed, the two molecules are *mirror images* of one another—one

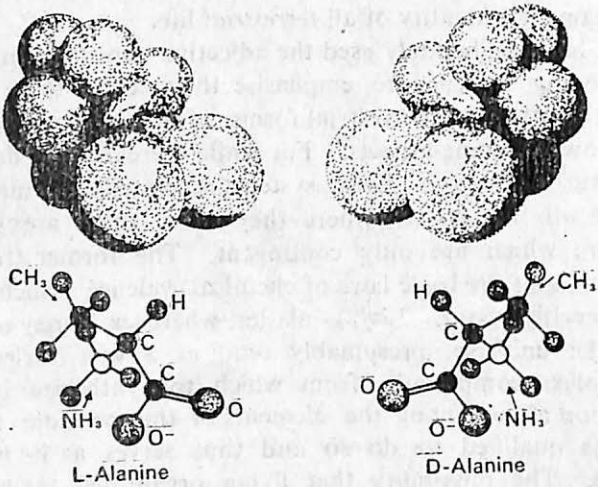


Fig. 1 : The stereoisomers of the amino acid alanine.

can be called the left-handed molecule, and the other the right-handed molecule. A most extraordinary fact is that all the proteins that have been investigated, obtained from animals and from plants, from higher organisms and from very simple organisms—bacteria, moulds, even viruses—are found to have been made of L-amino acids only.

Now right-handed molecules and left-handed molecules have exactly the same properties, so far as their interaction with ordinary substances is concerned—they differ in their properties only when they interact with other right-handed or left-handed molecules. The earth might just as well have been populated with living organisms made of D-amino acids as with those made of L-amino acids. A D-amino man, for example, would be very like his L-amino counterpart, except for left-right inversion. That is, he would write with his left hand instead of his right, his hearbeat would show his heart to be on the right side instead of the left, and so on. But he would drink water, inhale air and use the oxygen in it for combustion, exhale carbon dioxide, and carry on other bodily functions just as well—so long as he did not eat any ordinary food. If he were to eat ordinary plant or animal food, he would find that he cannot digest it. He could have been kept alive only on a diet containing synthetic L-amino acids made in a chemical laboratory. Nor could he have any children, unless he found a D-amino version of a woman with the same right-left inversion as his own. We thus see that there is the possibility that the earth might have been populated with two completely independent kinds of life—plants, animals, and human beings of two kinds, who would not have used one another's food, nor would have produced hybrid progeny. Nevertheless, these two forms of life would have been basically alike except

for the fortuitous difference that one would have been a mirror image of the other (Fig. 2).

Fig. 2 : Dextro man is the mirror image of levo man.

The fact, however, that living organisms have evolved in the L system rather than in the D system is apparently due to a biological accident. It has been suggested that the first living organism happened by chance to make use of a few molecules with the L configuration, which were present with D molecules in equal numbers. As a result, all succeeding forms of life that have evolved have continued to use L-amino acid molecules through inheritance of the character from the original form of life. This is a consequence of that remarkable property of life Jaques Monod has called *invariant reproduction*. That is,

the ability of living organisms to reproduce and to transmit *ne varietur* the information corresponding to their own structure. If the primeval Adam macromolecule I mentioned in the second article of this book happened by chance to be made of L-amino acids, all their subsequent progeny, the present plants and animals, could not help remaining levo, thanks to this invariant reproduction of life.

The persistence of only L-amino acids in proteins to the total exclusion of their D analogues seems to suggest that the ability of macromolecules of life to reproduce themselves *ne varietur* has had one common origin in the genetic code. It is via this code that the vast information required to reproduce biological materials is stored in the packages of genes, biologists call chromosomes. The chromosomes are in some respects like the punched cards of a computer, which carry instructions for making it work in the desired way. The only difference is that chromosomes are marvels of miniaturization for storage of information compared with punched cards. It has been estimated that the chromosomes of a single bacterium store around 10^{12} bits of information, comparable to about 600 million pages of this book! How this vast information is stored is still a mystery, now being gradually unravelled. But in principle the chromosomes are mere micro editions of punched cards in computer programming.

In order that the punched cards function as a source of information to guide the computer, it must be capable of spelling out specific messages in some alphabet just as letters of the English alphabet make meaningful words and words in turn make meaningful sentences. But the alphabet of the computer language is determined by the fact that it is essentially an assembly line of switches, relays or transistors. Each one of these components is

capable of exactly two states, 'on' or 'off', which we may designate respectively as the 'energized' or 'stimulated' state, and the 'de-energized' or 'unstimulated' state. If we denote the former by 1 and the latter by 0, any input signal in such a machine is a simple sequence of 0's and 1's. That is, the alphabet of the machine language in which its words are written is the binary set of symbols, 0 and 1. Its physical embodiment is the punched card with a set of holes bored therein with the hole corresponding to the energized state denoted by 1. That such a binary alphabet is adequate to write any message is obvious from the fact that a telegraphist uses precisely such a binary alphabet in transmitting any communication whatever, via the morse code with its repertoire of only two symbols—a dash (0) and a dot (1).

But just as a computer is an assembly of relays or transistors, a living organism is a collection of cells made up mostly of proteins. As already mentioned, proteins are large molecules composed of long chains of amino acids linked together by so-called peptide bonds. If we denote the known twenty-four amino acids by the letters B, P, Q, E, D, K, L, Q... a typical protein molecule could be expressed as a long chain of such letters as, for example the sequence:

—B—P—E—D—K—O—O—Q—

The information for the manufacture of protein molecule, like the aforementioned chain of amino acids, is carried in the genetic material popularly called DNA. The DNA itself is a complex sequence of four bases or subunits which we may denote by the letters A, C, G and T. Since there are only four bases or subunits in DNA as against twenty-four subunits (amino acids) of proteins, it is not difficult to see that a minimum of three letter

triplet is required to represent twenty four different amino acids. The four letters A, C, G and T each taken singly can represent only four amino acids. Even if we take them two at a time, there is room to make only $4 \times 4 = 16$ permutations which can represent only 16 amino acids against the required twenty-four. Taking them three at a time, however, yields $4 \times 4 \times 4 = 64$ different triplets out of four letters—a number more than the necessary minimum requirement of twenty-four.

We thus observe that a minimum of three letter triplet is necessary to represent all the twenty-four amino acids. Since there are now sixty-four available permutations, it happens that an amino acid is represented by more than one triplet. I will not dwell on the elaborate researches done to discover triplet equivalents of the twenty odd amino acids. Suffice it to remark that a knowledge of the base sequence in the DNA, and the resulting amino acid sequence in protein, gives away the code for each amino acid. In this way the four letter DNA alphabet A, C, G and T is able to spell out the entire dictionary of myriad protein structures written in twenty-four letter alphabet of amino acids. The correspondence between DNA triplets and their matching amino acids is now available in tables as precise and universal as the multiplication table.

The table below gives DNA triplets, or condons as they are often called, for two amino acids for the sake of illustration.

Table of genetic code

DNA triplet	*Amino acid*
AAA AAG	Phenylalanine
CTA CTG	Glutamic acid

The above table is only a fragment of the genetic code, the core of the basic unity of life. The equivalence between DNA, base triplets and their corresponding amino acids that it embodies is universal in all forms of life whether plant, viral, bacterial, animal or whatever. It is this information, taped in the DNA macromolecule according to the genetic code, that enables the cell to synthesize the proteins it requires. The information is conveyed to the sites in the living cell where proteins are actually assembled by a rather complex mechanism which virtually turns it into an exceedingly intricate automatic chemical computer fed on DNA tape. The analogy is, no doubt, rough and remote, but no more than other well known ones of animal physiology like the heart being a pump, lungs a pair of bellows, eye a camera, stomach a fermenter, central nervous system a telephone exchange, and so on. All such analogies, no matter how rough and remote, do have a degree of similitude that illuminates an aspect of their working. It is in this rough and remote sense that we may think of a biological cell as an automatic chemical minifactory, continually trading information (knowledge) for pattern (power) and vice versa, thereby demonstrating anew that knowledge is power as much *within* a molecule of life as it is without in the life of man.

Life, Our Biological Heritage : Its Manipulation 4

In the third article of this book, I described how the discovery of the structure of DNA, the material of which genes are made, set microbiologists searching for the genetic code. Our increasing knowledge of the gene and its coding properties has now encouraged the hope that it will enable us to manipulate biological evolution to produce not only better breeds of cattle and plants, but even of human beings. Whereas biological evolution has relied on random mutations and blind chance to produce the human species, the human species has now come of age to direct its own destiny by manipulating or designing mutations and deliberately eliminating blind chance. Some enthusiasts have even claimed that given any pre-assigned specification for the 'ideal' *Homo sapiens*, the new science or craft of genetic engineering will enable us to produce it. This is what is sometimes called 'playing God'.

The possibility of playing God was first mooted when it was found that 'engineered' gene replacements are feasible in simple unicellular organisms such as the bacterium *E. coli*, a miniscule organism normally present in human intestines ordinarily harmless and only occasionally pathogenic. It has been extensively studied by microbiologists during the past several decades. These studies have revealed a very complex hereditary apparatus of linked

genes packed in chromosomes. They have also shown that recombination of genes from different strains of *E. coli* may be achieved by a number of processes, some of which resemble the sexual fusions of ova and sperms in higher animals, while others involve a transfer of genetic material from one cell to another—a process that has not yet been successfully accomplished in any higher organism. Consequently, the mere fact that it is possible to modify the genetics of a bacterium such as *E. coli*, by inserting a synthetic gene or otherwise, is no guarantee that the same techniques may be applicable to organisms higher than viruses and bacteria. For there is a fundamental difference between lower organisms such as unicellular bacteria and multicellular higher plants and animals. Being single celled there is no separation between soma (body) and germ plasm in the former, as is the case in the latter. It, therefore, follows that exchange of genetic materials between cells of bacteria provides no basic reason for concluding that similar transfer is possible in the case of higher organisms.

Even in bacteria, whose reproductive cycle is measured in minutes instead of months, usually only a single factor or gene is transferred at a time. Double characters (e.g. capacity to ferment sugar mannitol and resistance to an antibiotic such as streptomycin) sponsored by two distinct genes may occasionally be transferred simultaneously if the two genes in question are close enough. But polygenic characters sponsored by several genes have not yet been transferred even in bacteria. No one yet knows whether or not the genetic make-up of higher organisms will be amenable to genetic manipulation by any means as, for example, by splicing a gene onto a virus and using the virus to infect a sperm or egg. It is quite likely that it may not be so amenable. For animal cells may for

evolutionary reasons be specially organized to resist this form of viral usurption. The present genetic engineering techniques in that case may well prove, in so far as higher organisms are concerned, simple dead ends.

The real truth is that modification of the genetic characteristics of any organism, even of a bacterium, is no simple matter. In the case of higher organisms such as plants and animals, the situation is naturally infinitely more complex. We need here to discover what Henderson has compendiously called the 'wisdom of the body'. Everybody alive, including the simplest bacterium, is a repository of the accumulated wisdom of 3000 million years of biological evolution on earth. It is likely that its subtleties will always remain beyond our ken. The much-studied simple *E. coli*, for example, has (among other things) to produce some hundreds of enzymes or biological catalysts in appropriate concentrations and precise spatial locations in order to stay alive. A mere description of how it carries out this fantastic feat of chemistry would occupy several volumes, if and when we came to understand it fully. Any single enzyme could be the theme for a near lifetime of good scientific work. Nor is this all. Even a complete study of all the enzymes it makes would not bring a molecular understanding of *E. coli* much nearer. The more we probe the molecular basis of life the deeper grows its mystery. We seem to face here a particularly vicious version of the law of diminishing returns, Sir Macfarlane Burnet has aptly called 'an asymptotic brick wall'. Which is merely to say that the effort tends to infinity as our understanding approaches completion, even in the case of such simple organisms as *E. coli*, let alone the higher organisms such as plants and animals.

But higher plants and animals are not simple unicellular organisms like *E. coli*. They must be studied at

three levels : (*a*) the molecular level, (*b*) the cellular level, and (*c*) the holistic level covering the organism as a whole. There are further complications due to diverse interrelationships between these levels. It, therefore, seems that the whole basis of the fantasy called 'genetic engineering' is far too flimsy at present to warrant the belief that spectacular breakthroughs in the production of cultigens, poultry and cattle far superior to those now being produced, are around the corner. We need to know much more about the heredity as well as cytology of plants and animals to manipulate their biological inheritance to our advantage in any meaningfully *predictable* way. We can perhaps come by such knowledge only by very careful combined work by geneticists, biochemists, microbiologists, animal breeders, agronomists and many other specialists—work which in its early stages will appear too academic and abstract to be of any immediate practical use. It will be long before it can be applied.

For the time being, therefore, genetic engineering will be confined to the domestication of more and more bacteria for the benefit of man by hit-or-miss methods, rather than predesigned or specially contrived mutations. Nevertheless, such hit-or-miss methods, time consuming as they are, do sometimes produce useful results. For example, it is already possible to 'command' the bacterium *E. coli* to produce the harmone, somatostatin. In this way, bacteria can be increasingly turned into 'factories' for the production of more complex and useful biological proteins, ranging from insulin and other harmones to the enzymes used in industrial fermentation. The insulin breakthrough, in particular, would be a boon to millions of diabetics, not merely because it would be a lot cheaper, but also because this insulin would be an exact replica of human insulin, thus eliminating the risk of allergy or

antibody-rejection of the currently used pig and beef insulin.

Other anticipated more immediate rewards of genetic engineering include safer, more potent vaccines, microbial strains capable of producing larger quantities of antibiotics, and nitrogen-fixing plants, which could dispense with the use of energy-guzzling synthetic fertilizers. The latter possibility seems quite real even though there do not exist any plants at the moment that can fix nitrogen. However, there are a large number of plants which have bacteria associated with their roots, and the combination can fix nitrogen. One of the nicest things one could do is to make plants that could fix nitrogen without having their bacterial associates. This is a long term objective and we still do not know when it will come to pass. Nevertheless, transfer of the nitrogen-fixing genes from those bacteria that have them, to those that never had them before, has already been accomplished. Researchers have succeeded in getting the nitrogen fixation genes on to a small genetic element which transfers itself very readily between one kind of bacteria and another. The way is thus open to try to put these genes into plants.

We may, therefore, reasonably look forward to some of these simpler genetic engineering potentials actualising in the next two decades, now that the initial scare of its attendant biohazards caused by the Berg letter* published a few years ago, has died down. The scare that led to guidelines for the conduct of genetic engineering research,

*Letter published by Paul Berg and eleven other distinguished scientists in the 24 July, 1974 issue of *Science*, the journal of the American Association for the Advancement of Science. It recommended a voluntary renunciation of certain kinds of genetic experiments until the potential hazards of recombinant DNA molecules had been properly evaluated.

and proliferating bureaucracy to enforce them, did inhibit such research during the past few years. But it is now being increasingly freed from these restraints because the hazards have been found to be greatly exaggerated. Given sufficient time, the knowledge to manipulate the stuff of life—the ultimate technology—may not prove that elusive after all. It seems likely that some decades hence, genetic engineering may advance slowly by suggesting to agronomists and animal breeders better ways of improving crop plants and domestic animals. Next will come a development that may be opposed by some, who, like George Wald, advocate that the human genome be declared inviolable. As the development in question, however, will be the genetic treatment of some of the 1500 human diseases now known to be of hereditary origin, it will almost certainly manage to secure at least a toehold, if not a foothold, on humanitarian grounds. Once genetic engineering technique is able to circumvent the genetic manifestation of deleterious human genes, means of genetic manipulation may then be discovered to produce more intelligent, or more docile, human beings as envisaged by Aldous Huxley in his *Brave New World.* We cannot tell which. But all this is as yet a distant dream—the possibility of genetic manipulation of forms of life higher than bacteria not having been yet demonstrated.

Life on Other Worlds 5

The essential uniformity of behaviour of atomic particles throughout the wide universe poses an intriguing question: if some terrestrial atoms somehow managed to cast themselves into the human mould, could they not wake to a similar ecstacy of life and consciousness in other celestial habitats besides our own earth? Many man-made myths from Micromegas, Selenite and Bel Abon to mooncalf pastures, Martian canals, Bermuda triangle, flying saucers, and 'bug-eyed monsters' from interstellar space testify to the continual persistence of a naive belief in the power of life to irrupt in extraterrestrial abodes, as unlike one another as Sirius, our Moon and Mars.

There is a school of thought prevailing even now that has a sort of mystic faith in the fitness of almost every celestial environment to develop and evolve its own species of living beings whose bodies and organs are supposed to be adapted to the peculiar circumstances of their particular abode. Even the strictly disciplined and controlled imagination of that great imaginer, Olaf Stapledon, could not resist the temptation of toying with the idea that life and intelligence could perhaps emerge and persist in incandescent environment of stars in the form of myriad self-conscious flames of life. At the other end of the spectrum of beliefs there are some eminent biologists such

as W.H. Thorpe, who think that the emergence of *cellular* life from inanimate matter is a happening 'now seen as so extremely improbable that its occurrence may indeed have been a unique event of zero probability'. With informed opinion oscillating between two extremes—one holding life's emergence as a virtual 'miracle' due almost to divine intervention, and the other as the inevitable consequence of the laws of physics and chemistry—is it any wonder that the existence of extraterrestrial life is for many people a touchstone of their hopes and desires? Those who want it will choose the latter point of view and those who don't the former. There is therefore need for as unbiased an approach to the subject as one can make it.

To make a realistic appraisal of the possibility of extra-terrestrial life, one must begin by defining what one means by 'life', considering the great profusion of life on earth from the barely alive viruses to the highly intelligent human beings. By 'life' I shall mean here 'carbon-based life as we know it' that is both *intelligent* and *self-aware*. This will exclude all those primitive forms of life of which microorganisms such as viruses and bacteria are the prime examples. There might well be planets—Mars is a possible case in point—barely capable of harbouring only such a primitive and lowly form of life. But I will ignore them as 'lifeless'. Again there might well be planets which could support some unknown form of life with a chemistry different from that of our own on earth, which is structurally based on carbon and utilizes water as an interacting medium. It could instead be based, for example, on silicon for structure and/or use liquid ammonia as an interacting medium. Thus one could envisage beings living in seas of liquid ammonia on Jupiter or breathing gaseous sulphur on Mercury. Again I shall dismiss such forms as mere science fiction fantasies. They do not apparently

qualify even as plausible biological 'perhaps' so far as we can imagine at present.

In our search for an abode suitable for the emergence of *intelligent, self-aware* 'life as we know it', temperature is a reasonable starting point. For life is an attribute of matter that appears only in highly complex and therefore correspondingly fragile structures. Even a protein molecule, not to speak of other more elaborate structures such as cells and animal tissues, is a complex and delicate entity extremely sensitive to heat. No living tissue, cell or bacterium seems able to withstand even boiling water. The hottest niche that living organisms have so far been known to occupy is in Yellowstone Park where bacteria have learnt to survive in hot springs at 76°C, but none have been found in any of the hotter natural springs in spite of life's incredible resourcefulness to colonize any possible ecological corner. Apparently 80-90°C is a fundamental upper limit to which life can accommodate itself. For intelligent life such as human life, it is much lower. We may therefore rule out all possibility of life in any of its variety and adaptations in the stars, as even the coolest of them have surface temperature of 3,000°C—much too high for any except the simplest compounds to exist. But if excessive heat inhibits life of all kinds, too much cold is equally fatal. Vital processes—as our experience here on earth shows—depend ultimately on the energy received from the Sun. If this supply had been much smaller, it is doubtful if life could have ever been sparked out of its inanimate slumber. It therefore follows that only planets located at just the correct distances from their central star to give them the right amount of starshine and warmth, can be suitable abodes of life in any possible form. If they are too near their central star, no life can originate in the midst of hell fires to which their close proximity exposes

them. On the other hand, if they happen to be too far away, life may remain congealed for ever in the frosty cold of outer space.

But it is not merely their distance from the central star that has to be right. So must be their other features such as mass, axial rotation, atmosphere, hydrosphere, ellipticity of orbit and so on. Thus if a planet or satellite like our own moon fails to combine the right blend of these other conditions, its location at the right distance from the sun will be of no avail. For the moon, having too small a mass to retain any atmosphere, is both airless and waterless. It is therefore lifeless as the U.S. astronauts who landed on the moon in 1969 discovered.

Not only must the planet be at the right distance from its central star, it must also have the right mass. For, if a planet is too massive, its gravity may be too strong to permit the emergence of life, at any rate intelligent life such as human beings on earth. The reason is that excessive gravity inhibits physiological and metabolic processes of animals as large as ourselves. Even though we can endure indefinitely the earth's gravitational pull, usually denoted by the acceleration *g* caused by this pull, experiments with human beings in large centrifuges simulating accelerations of the order of 5*g* have shown that we can tolerate such high *g*'s for very brief periods of time, without permanent damage. A tolerable upper limit seems to be 1.5 to 2*g*.

Then again, if a planet's orbit is highly elliptical, as in the case of Mercury, the seasonal variations in the intensity of solar radiation may prove too great for life to develop and take root. Thus Mercury at its closest approach to the sun receives two and a half times as much sunshine as at its furthest. This alone gives rise to too violent fluctuations of temperatures. To make matters

worse, the violence is fantastically amplified because of the coincidence of the period of its axial rotation with that of its revolution round the sun. As a result it presents approximately the same face to the sun as the moon does to the earth, so that it is a fearful furnace of molten lead, lava and tin on the sunny side and an equally terrifying Cimmerian nightmare of frozen gases on the other eternally dark, unlit side. These conditions, whose rigour is in a way, mitigated because of the virtual absence of wind and water, prevent it from harbouring life of any kind whatever. It is therefore no wonder that hardly one (that is, our own earth) out of the nine planets and their numerous satellites of our solar system have managed to acquire the right combination of conditions that provide a possible home for intelligent life. To find a possible abode of intelligent extraterrestrial life we must go beyond the solar system and look for planets of the stars beyond.

When we consider that barely ten per cent of the stars in our Milky Way are born, like our own sun, single and not every such star has a planetary system, and further that only 10 per cent of its planets may acquire the right blend of mass, axial rotation, distance and other attributes likely to favour the emergence of life and intelligence, we may well appreciate how scarce and lonely life must be, wherever in the universe it may have chanced to sprout. Assuming as a rough reckoning that not more than one star out of a hundred thousand taken at random can possibly have a planet with intelligent life on it at some particular stage of development, there may well be a million or two inhabited planets in our Milky Way consisting of 200 billion stars. If there are, indeed, a million or two planets harbouring intelligent life, some of these forms of life would be much more advanced than ours, considering that our technical civilization is barely two

hundred years old. Why then have we not had any intimation or message from them proclaiming their existence? It has been suggested that we have not heard anything from more advanced 'civilizations' in the Milky Way, because advanced technical civilizations always destroy themselves through the use of weapons of mass destruction shortly after they come into being. If such civilizations do destroy themselves soon after their emergence, as ours is threatening to do, then there might well be in the second half of the 20th century in the galaxy, only one technical civilization—our own.

But if, on the other hand, we assume—not unreasonably—that other technical civilizations in the Milky Way are not as foolishly suicidal as our own, and do manage to avoid self-annihilation, by control of their megakill weapons, then the lifetimes of technical civilizations may be very long, comparable to geological or stellar evolutionary time scales. If so, there may well be a million technical civilizations extant in the galaxy now. If they are randomly distributed in space, the distance from the earth to the nearest such civilization will be several hundred light years. The only way we could communicate with it is by means of radio transmission, even though other communication techniques have been seriously discussed.

To take the latter first, several types of spacecrafts have been proposed to take us to the stars. They are nuclear pulse rockets such as the British Interplanetary Society's *Daedulus*, the interstellar ramjet which collects fuel from interstellar space, the laser-photon sail, antimatter devices and the legendary photon rocket whose exhaust is a beam of light and thus enables it to travel at almost the speed of light, the putative speed limit of the Universe. There are suggestions that we could even transcend this limit by travelling faster than light or at

least popping down a black hole and out again instantly into another remoter region of the Universe. Alas, both faster-than-light travel, as well as black hole rapid transit system are at present pure science fiction fantasies. Nevertheless, some of the more orthodox devices such as *Daedulus* and ramjet may not be wholly impractical. But if the measure of effectiveness is the amount of information communicated per unit cost, then radio transmission is the method of choice.

With our present equipment we can communicate by radio up to 1000 light years. This may seem small in so far as stellar and galactic distances go. But it is a large enough range to contain scores of technical civilizations if the surmises made earlier are correct. The problem is how to establish such a radio link with them in the absence of a common language. It is a serious problem though not wholly insurmountable, for, in the absence of a common language, there are messages whose intelligent origin and intellectual content could be made very clear without making many anthropocentric assumptions. Because of the expectation that our own civilization on earth is comparatively young and therefore relatively very backward, it does not make very much sense to transmit messages to hypothetical planets of other stars. But it may very well make sense to listen for radio transmission from planets of other stars. Project *Ozma*, a very brief programme of this sort, oriented to two nearby stars, Epsilon Eridani and Tau Ceti was organized in 1960 by the American astrophysicist F.D. Drake. It drew a blank. Its failure is no great surprise. It does seem very unlikely that success would greet an effort aimed at two stars only twelve light years away. It remains, however, the first pioneering attempt at interstellar intercommunication. Although related programmes on larger scale have since

been organized, they too have not been successful.

The search for extraterrestrial intelligent life is an extraordinary pursuit. If we do stumble to it, it is very likely that the technical civilization it has built for itself is by far more advanced than ours. An encounter with such an advanced technological civilization will bring rich rewards. It will provide answers to many scientific riddles such as that of black holes, origin of the universe, of stars, of life and intelligence that baffle us no end today. It might also show us the way to solve the political problem of self-annihilation that we seem unable to resolve at present. But even if we encounter a civilization no more advanced than our own, the quest will still be worthwhile. It will at least assuage the fright, which, according to Pascal, often seizes us when we contemplate 'the eternal silence of the infinite spaces' of the Milky Way and beyond. It will be some comfort to know, if we ever do, that we are not alone in the wide universe around us.

Heredity and Disease 6

When Shakespeare wrote about a 'mildewed ear blasting his wholesome brother', he had a clear premonition of what we now call infection. Yet three centuries later, the famous botanist, Professor Lindley, when confronted with the potato blight which brought famine to Ireland in 1846, put the cart before the horse and held that mildew was the consequence and not the cause of the disease. He continued to believe that the diseases of plants were 'plainly and directly hereditary'. The temptation to attribute the unknown cause of disease, whether of plants, animals or men, to some still more unknown factor such as heredity was the type of *obscurum per obscurius* that was a favourite pastime of learned scholars at the time.

Recent advances in biochemistry, genetics and medicine have shown that there are two broad types of diseases, one due to the impact of outside infection (environment) on the individual, and the other due to some genetical abnormality that the individual may inherit. Besides these two types of diseases, there are quite a number which are betwixt and between environmental and genetical diseases such as schizophrenia and other mental conditions, which seem to arise only if the genetical predilections one inherits show themselves in an adverse environment.

What is even more important is a person's whole

genetic makeup—his complete genotype—in relation to almost every disease, and, in particular, its virulence. For even when a condition is largely environmental, individuals who differ genetically will react to it in different ways. A strong constitution like that of Casanova or Schopenhauer may live almost up to Psalmists' three score and ten despite syphilis, while another like Henry VIII or Nietzche may succumb to it in comparative youth. The most striking difference in this respect is that between males and females.

Even though woman is considered the 'weaker vessel', it is the male who is far more vulnerable to most diseases and defects—almost all except those which are chiefly glandular or which are peculiar to females. She is genetically more robust because she starts off with two X chromosomes (one from each parent) while the male gets only one X from his mother. The other chromosome Y from his father is only an atrophied one with very few genes. Accordingly, if any lethal or semilethal genes are in the male's X chromosome, it is usually far more dangerous for him than it would be for his sister, even if she inherited the very same X. The defective gene will usually be suppressed by a normal gene in her other X. The poor male with his atrophied Y chromosome has no spare to quell the aberrant gene, in his single X. This is why certain sex-linked diseases such as haemophelia afflict only males. Females are only its carriers.

However, defective genes are not merely confined to sex-linked chromosomes which make males more liable to certain kinds of hereditary afflictions. They may arise equally on other chromosomes. When they do, the upshot is a hereditary disease to which both sexes are more or less equally prone. Genetic diseases may also arise from purely chromosomal aberrations, even when the genes

they contain remain normal. About six per cent of children born alive show recognisable genetic defects, either because of an aberrant gene in a chromosome, or an aberrant chromosomal arrangement.

An instance of chromosomal irregularity is the birth of children with abnormal combinations of sex chromosomes instead of the normal combination XX (female) or XY (male). All these abnormal types have subnormal intelligence. Their abnormalities are incurable. No genetic engineering technique has yet been devised to make an XO inter-sex into a normal woman by adding the missing X, or removing the unwanted Y from the criminal hypermale XYY or X from the nancy male XXY.

Far more interesting are genetic diseases due to a single defective gene in a chromosome. A case in point is sickle cell anaemia which arises due to an aberrant gene that produces an abnormal variant of haemoglobin. This variant can carry only half the normal amount of oxygen from the lungs to the diverse parts of the body. Consequently, if both the genes the individual inherits from its parents are defective, it diəs of sickle cell anaemia. But if it inherits only one defective gene, the other gene from the second parent being normal, it is only half anaemic. However, the debility has its compensation. It enables the recipient to resist malaria, better than the normal individual and thus survive. Natural evolution seems to have deliberately distorted human haemoglobin molecules to spite the malarial parasite. That is why this debility most commonly occurs in the malarial regions of Central Africa.

In general, a defective gene inhibits the production of specific metabolites, and specially the specific proteins or enzymes responsible for some of the myriad metabolic functions of the body. In the absence of the enzyme,

the metabolism of the cells is altered, with consequences that may be harmless, injurious or lethal, depending on the importance of the chemical reaction catalysed by the enzyme in question.

For example, a rare mutation in human beings is associated with the loss of an enzyme necessary for the normal degradation of glactose, a constituent of lactose, or milk sugar. For individuals with this mutation, milk is a toxic substance, because glactose accumulates in tissues when lactose is ingested. The accumulation of glactose gives rise to a number of clinical effects such as enlargement of the liver, development of cataracts and loss of weight by the patient. Since lactose is generally absent in foods other than milk, these deleterious effects of the injurious mutation can be avoided simply by abstaining from milk.

A score of diseases have already been recognized as enzyme diseases caused, like sickle cell anaemia, by the manufacture of abnormal molecules in place of active enzyme molecules. It is not unlikely that there are hundreds or thousands of such diseases. This is why enzymology, with its accent on the molecular basis of human disease, is likely to be the keystone of the arch of medicine and pharmacology of the future. Indeed, as Linus Pauling has predicted, one day when our understanding of enzyme activity has advanced sufficiently, many of these diseases will be treated by the use of artificial enzymes, specially synthesised to catalyse the biochemical reactions within the diseased body; which its malformed enzymes fail to sponsor or support.

Heredity and Blood 7

Before the discovery of genes and chromosomes around the turn of the century, heredity and blood were by popular consent as closely tied as cause and effect. Heredity was merely a consequence of the passage of blood—the blended blood of both parents—to the progeny. The view harks back to Pythagoras who had speculated around 500 BC that human life begins with a blend of male and female fluids or semens originating in body parts. Aristotle later postulated that the semens were purified blood, and blood therefore is the carrier of heredity. If it happened to be 'noble', 'royal', 'blue', or 'pure', the offspring would be brave, beautiful, bright and brilliant. But if it was 'common', 'base', or 'plebian', he would turn out to be criminal, ugly, shifty and depraved. It was this *vox populi* that Thackeray echoed when he made James Crawley in *Vanity Fair* say: 'Nothing like blood, Sir, in horses, dogs and men'. We now know better. *Vox populi* that Crawley echoed was not *vox dei* but the voice of ignorance and prejudice. For it is not blood that passes from parent to progeny, but packets of genes wrapped in chromosomes. Blood is as much the outcome of the chain of biochemical reactions sparked by the inherited genes, as any other tissue or organ of the body. Consequently, even a mother and her child do not share a single drop of blood although

she carries the fertilized egg during its nine-month long gestation. Indeed, in some cases, she may even unwittingly kill the baby if her blood contains a hereditary something, the so-called Rh factor, which is hostile to that in her baby's blood. It is just as possible for two persons in a family to inherit different kinds of blood, as it is for them to inherit differences in eye colour or other physical traits. The reason is that the type of blood an individual inherits is, like the colour of his eye or skin, wholly genetical regardless of the environment.

It happens that while the choice of eye or skin colour that the genes concerned have, is rather limited, that of blood types that the sponsoring genes provide is practically unlimited. The skin colour may be white, black, honey yellow, brown, mulatto, or copper. But blood types are almost as numerous as the number of possible genotypes. The blood type of an individual may be group B with regard to one factor and group M or MN with regard to another. It may be Rh positive, Kell negative, Duffy positive, and so on, with regard to yet other factors. Since each factor gives rise to at least two variations—positive and negative depending on the presence or absence of the factor in question—n factors yield 2^n different types of independent blood group systems. Thus, with 10 *independent* blood factors, there are 2^{10} or 1024 different combinations possible. With an additional 10 blood factors, the number of combinations swells to 2^{20} or 10,48,576. Considering that 11 independent blood factors are already well established, in addition to as many as 70 new factors claimed to have been detected or assumed to exist, the number of combinations possible among general population is inconceivably large. It is so huge that many of these possible combinations, like the possible genotypes, have not even existed on earth.

The reason for the great variety of blood factors is the fact that although the red blood cells of all normal human beings look alike, they are chemically very different. Each individual's red blood cell carries a set of chemical substances called antigens, which vary in type in different individuals, and to some extent in different races. It is the discovery of antigens in red blood cells that has revealed the extraordinary built-in defence system of the body, we now call *immunity* against invasion by foreign microorganisms that continually strive to enter from the outside and infect the body with disease. We now know that disease and disability may be divided into two categories with only a minor residue that remains indeterminate. There are diseases which result from the impact of environment on individuals who are otherwise genetically normal, and on the other hand, diseases which spring from some genetical abnormality that the individual may inherit. Nearly all diseases and disabilities of the first kind, except those which may be caused by malnutrition or physical injury, arise from outside infection by harmful bacteria and viruses that somehow enter the body of the individual. It is against such invading microbes that the human body has, during aeons of evolution, built up a natural defence system. For instance, the air we breathe is filtered in the nose, where a large portion of microorganisms it contains are caught in mucus and ejected through the nostrils. But besides such purely mechanical barriers, the body also resorts to much subtler chemical warfare to destroy, or at least render innocuous, those foreign microbes or cells that do somehow manage to enter it. It does so by producing certain substances within the body to make itself immune from the toxins or poisons formed by the invading microbial hosts. If it recovers from the injury inflicted by the invaders, it

acquires an immunity from further harm. Such, for instance, is the case with diseases such as small-pox, measles, mumps, etc. which are caused by viruses, or those such as typhoid and diptheria, which are caused by bacteria. A person who has once suffered from these diseases becomes immune to subsequent attacks, provided, of course, he survives the first. But the immunity conferred is specific, not universal; an attack of measles protects against measles but not against small-pox and vice versa.

The specific immunity that the attack confers may also be acquired by deliberately exposing an individual to a mild infection. This discovery of acquired immunity was made by many early pioneers in immunology, men such as Jenner, Pasteur, Kock, von Behring, Ehrlich and others. They showed that immunity against infectious diseases could be induced in people by active administration of killed or attenuated microbes and their products, as effectively as by natural, if more virulent, infection. The methods of prophylactic immunization they devised simply involved imitating natural infection in a controlled manner. There were, of course, many tricks to learn about how to prepare suitable immunizing materials—the vaccines and sera. But they were learnt by empirical means without any knowledge of the immunizing system at work within our bodies.

Although immunity is still thought of in the context of infectious diseases such as small-pox, cholera, diptheria, etc. contemporary immunologists have now moved on from the days of empirical immunization by vaccines and sera, to the discovery of the mechanism underlying what has turned out to be a highly complex and sophisticated defence system. Theory and practice are at present concerned with immune responses against alien cells

placed in the body by surgical transplantation, or arising in the body as incipient or established cancers. The practical problems that call for solution are to ensure that a kidney transplant is not rejected by the immune response, or to accentuate an inadequate immune attack on a malignant tumour. They require a deeper probe into the uncanny capacity of the body to recognize the intrusion of material foreign to itself, be it a virus, bacterium, cell or whatever, and to mobilize cells and cell products to help remove that particular sort of intruder with greater speed and effectiveness.

The complex defence system of the body has four main participants; antigens, antibodies antigen-antibody binding and white blood cells. The interaction of these participants is most simply understood in terms of an analogy; a potential criminal appears but is handcuffed by the police in the nick of time and rendered innocuous by imprisoning him in the local jail. Read for the putative criminal, an antigen, for police, an antibody, for handcuffing of the villain, antibody-antigen binding, and for imprisonment, phagocytosis, or cleanup of the bound antibody-antigen complex by white blood cells. This analogy, though rough and remote, works after a fashion in the following way.

An antigen, the analogue of the villain, is any substance capable of evoking the immune response of the body. It is a tell-tale molecular marker, most often a protein or a polysaccharide (a complex carbohydrate), both of which are important constitutents of several bacteria and viruses. An antibody, the counterpart of police, is a matching molecular pattern, usually a complex protein structure that is able to bind itself to an antigen and thereby neutralize it. For producing antibodies, the policemen of the body's defence mechanism,

two systems of cells have been evolved. In the body, they both arise as descendants of stem cells in the bone marrow. They have no immune properties until they have entered and multiplied in an appropriate organ. One such organ is the thymus. There the cells develop and become adapted for their special role as immunocytes of the thymus-dependent or T-series. The othes site is not yet known in mammals. It may be somewhere along the intestinal tract from tonsils to appendix, or it may be in the bone marrow itself. These cells become the B-series of immunocytes.

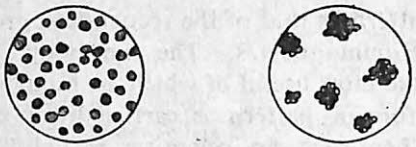
Both B- and T-cells carry miniscule 'photographs' of potential villians to identify them. These 'photographs' are patches of what we have called antibody on the surface of the cells. Soon after a baby animal is born, both series develop a great diversity of antibody patterns but only one pattern per cell. The subject of antibody is far too complex to discuss here in detail. Suffice it to say that when a T-cell meets a chemical pattern X, usually on the surface of another cell, it recognizes it instantly because the pattern X and its own immune pattern fit in a complementary manner, like a key fitting its lock. Things begin to happen in the wake of such recognition. The T-cell is stimulated to proliferate and produces a family of descendant T-cells, all carrying the same immune pattern. When such cells now meet a group of cells carrying pattern X, the T-cells attack and, if all goes well, eliminate their target cells.

The B-cells have a different approach. Their method of recognizing a foreign pattern in the body is probably basically similar, but their response is quite different. They multiply and in the process change to a plasma cell clone. Basically a plasma cell is a highly specialized factory for synthesizing and liberating antibody protein,

each molecule of which is identical and carries precisely the same pattern as that of the recognition groups on the ancestral B-immunocytes. The antibody has several functions, the most useful of which is brought into play when the foreign pattern is carried by an invasive bacterium. When such an organism is lightly coated or 'opsonized' with antibody, it is much more effectively taken in and destroyed by the phagocytic cells of blood and tissues.

The essential difference between the two systems is that T-cells act *as* cells attaching themselves to and destroying their target cells. Their action is also spoken of as cell-mediated immunity, and they are mostly concerned with foreign *cells*. The B-cells are primarily producers of soluble antibody and although antibody can be produced against any form of foreign pattern, including those on transplanted or malignant cells, its main value is in protection against bacterial infections.

These principles of immunology govern the genetics of human blood groups. We have already seen how various independent systems of blood groups such as O, A, B, Rh, MN, etc. arise because of the presence of certain chemical substances, called antigens, in red blood cells. The antigens make the red blood cells clump together like bunches of grapes, if and when they come in contact with other chemical substances called antibodies, carried in the fluid part of the blood, the plasma or serum (see Fig. 1). But again this antigen-antibody reaction is highly specific, like that of a lock and key. Just as a key will fit only its own lock, so also an antigen in red blood cells will make them clump together *if and only if* it comes in contact with its own associated antibody in the blood plasma and not otherwise. Obviously, therefore, an antigen and its corresponding antibody cannot normally



(*a*) (*b*)

Fig. 1 : Appearance of red blood cells. (*a*) In normal condition. (*b*) When 'clumping' in the presence of blood serum containing the associated antibody takes place.

coexist in the same individual. It is this property of an antigen to react with its associated antibody that makes indiscriminate blood transfusions so dangerous. If an individual whose red blood cells carry an antigen such as A, were to donate his blood to another, the recipient's blood serum may contain the specific antibody, anti-A, associated with A. If so, the donor's red blood cells will clump together and block the recipient's capillaries often resulting in his death.

Arthritis—is it self-induced affliction?

Arthritis, probably the second most common and distressing affliction of the elderly, is a disease of the joints. It causes considerable pain, discomfort and lack of mobility, making life an almost unbearable burden. Worse, it is often a prelude to other ailments. Treatment has been limited to steroids (such as cortisone) or, more recently, a fast-growing number of aspirin-like anti-inflammatories. Either family is merely a palliative. It does no more than relieve symptoms. Neither is free from side effects. What is needed is a drug that really cures and is not a symptom suppressor.

Recent research in immunology, discussed above, provides a clue to a possible cure. It suggests that

arthritis may well be self-induced, in that it is an abnormal response to injury by the body's own immune system, the most important defence mechanism against biotic invasion.

Suppose a joint is injured. The body's immune system immediately spots the debris of the injury as a potential 'criminal' alias antigen to be hauled up so that the process of healing can go unimpeded. And the clean-up process itself involves the intimate cooperation of both types of 'policemen', the B- and T-cells. The process begins with the immune system spotting the antigens on the surface of the offending debris. B-cells then produce antibodies that bind to the foreign antigens, forming what are called antigen-antibody complexes. T-cells perform a variety of functions, including the priming of macrophages to make them effective scavengers. The macrophages finish the job, engulfing and cleaning up the antibody-coated debris.

If even one link of this interacting chain of reactions is broken, the immune response goes astray. In arthritis, it is now surmised, the problem may lie with the T-cells that prime the macrophages for the final scavenging step. The consequences of the immune malfunction are two. First, the initial cause of the injury is not removed. Second, powerful enzymes from the macrophages spill into the joint cavity where they attack healthy tissue. Hence the bone deformation and distortion of the joint familiar in arthritis.

Drug companies are now busy devising new drugs that seem to work by rectifying the aberrant T-cell activity. One such candidate with anti-arthritic potential is Johnson and Johnson's Levamisole, originally developed as an anti-parasitic agent. Another is its new drug TP-5 which has reached the clinical trial stage in America and Europe. There are other candidates too in the field. But

they are still in the animal testing stage. They are France's Laboratoire Servier and Pierre Fabre with their drug called Cyclo-immune and F1686 and America's Wyeth with its Wy1825. If any of these candidates do succeed, arthritis patients may not be the only beneficiaries, for malfunction of the immune system plays an important role in the incidence of many diseases. It may well be a pointer to their cure as well.

The Chemistry of Abundant Life 8

Ever since man's emergence on earth, disease and destitution have been his perennial afflictions. They have possessed him like the demons and all but drowned him in a sea of sorrows. As the Bible said long ago, 'in sorrow thou shalt bring forth children' and 'in sorrow shall thou eat, all day of thy life'. It is therefore no wonder that early man should have sought refuge from his pains and privations in prayer or its secularised counterpart—the pipe dream.

A persistent pipe dream of the ancient world was the Alchemic Myth that retained its credibility till the dawn of scientific revolution in the 17th century. It is belief in such will-o'-the-wisps as philosopher's stone and elixir of life. While one was early man's nostrum for ridding poverty, the other was a putative cure for all his ailments. Very often the alchemic dreamer did not bother to discriminate between disease and destitution and dreamt a single panacea for both. It was the philosopher's stone and elixir of life fused into one.

As recently as the 17th century the anonymous author of the *Sophic Hydrolith*, for example, gave a recipe for synthesizing an alchemic ombudsman that would exercise both disease and destitution at one stroke. He concluded his account with the claim that the stone 'thus prepared

included all temporal felicity, bodily health and material fortune. By its aid, Noah built the ark, Moses the tabernacle, Solomon the temple, all three acquiring fabulous wealth and abounding health in the bargain'.

Although Alchemic Myth was no more than day-dreaming in response to some basic psychological urges of the human mind, it nevertheless did have very salutary side-effects. For in their endeavour to make gold and elixir, the alchemists paved the way for later-day development of science and technology which now enable us to make a wide variety of materials to meet specific human needs. We have already begun to make synthetic fibres, rubbers, detergents, paints, absorptive resins, dyes and drugs. These are examples of what modern alchemy (chemistry) can do in imitating and improving natural products.

The next stage is the synthesis of materials on the basis of theory so that they have desirable properties not found in their natural analogues. For we now have the means to manipulate atoms and molecules as scientists of the earlier century were able to manipulate levers, cogwheels and cylinders.

One of the techniques of molecular exploration is X-ray crystallography. For it is a form of microscopy without a microscope ! It has provided scientists with a novel type of artificial vision whereby one could perceive—though not precisely 'see'—things of extreme minuteness like the separate atoms making up a molecule. The method of doing so is delightfully simple in concept though often exasperatingly difficult in practice. The beam of X-rays, passed through a crystal of the substance under examination, produces a pattern upon a film. It cannot do anything more because there are, up to the present time, no materials from which lenses can be made that will focus X-rays in the way a lens in a microscope focuses rays of light and

magnifies the resultant image. But the function and behaviour of the missing and unobtainable magnifying lens can be imitated by resort to a mathematical device called Fourier transform.

Fourier transform is based on the fact that there is one-to-one correspondence between the arrangements of atoms in the crystal (or solid) and the X-ray pattern it produces on a film. If everything is known about either of them—a big 'if' this, in most cases—the other is completely determined. This is why the X-ray pattern yielded by the crystal is virtually a coded blueprint of its molecular structure. It enables one to ferret out the secrets of the inner and invisible anatomy of molecules and thus make three-dimensional representations (usually in the form of plastic models or maps like the one shown in Fig. 1), locating the position of every atom which goes into the making of the molecule in question exactly as if this submicroscopic organization has been literally magnified to visible range. This is X-ray crystallography, an elegant concept, and quite evidently a powerful one, if what one has in mind is discerning what is otherwise indiscernible.

An even more powerful tool is probing molecular structures by means of neutron beams instead of X-rays. You fire a beam of neutrons (subatomic particles) instead of X-rays at the selected target and then watch how they scatter when they hit it. Although the trick is done more cheaply with X-rays, neutron beams have big advantages over X-rays. Whereas X-rays tend to bounce off the surface layer of atoms of a structure, beams of neutrons can penetrate deeper, thereby showing up details of its molecular structure including such aberrations as tell-tale symptoms of fatigue beneath the surface. They can penetrate right through the outer shell of electrons to the nucleus of an atom. They can reveal variations in the magnetic pro-

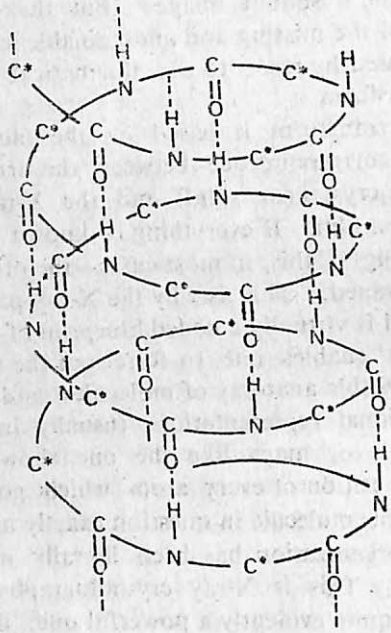


Fig. 1 : Three dimensional model of a complex molecule developed with the help of X-ray crystallography.

perties of atoms. Moreover, they tend mostly to bounce off the lighter atoms in a structure such as the hydrogen and carbon atoms important to biologists and chemists. X-rays tend to bounce off the heavier elements.

Exploration of molecular structures by X-rays and neutron beams has given a new dimension to material making. Take, for instance, the development of new drugs. The traditional hit-or-miss approach involved screening of hundreds or thousands of compounds, coming up with a likely-looking one and then finding out what, if anything, it could do. The new approach is to look hard at the

molecular mechanism behind a disorder and then design a drug specifically targeted against them. It has already begun to yield a new class of clever drugs.

A classic case in point is that of bacterial sulphanilamide which inhibits the bacterial enzymes concerned with the growth of disease-producing bacteria called streptococci. These bacteria require for their growth bacterial vitamin bearing the unwieldy name of para-aminobenzoic acid which I will abbreviate as PABA. PABA apparently acts as a substrate for some bacterial enzymes. But as the molecular structure of PABA happens to be similar to that of sulphanilamide (see Fig. 2), sulphanilamide competes

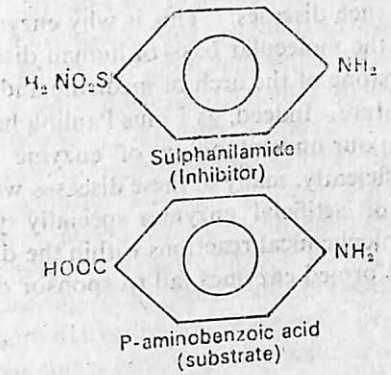


Fig. 2 : Molecular structure of PABA.

with PABA molecules for the capture of the active site of the bacterial enzymes. Consequently the bacterial enzymes react with sulphanilamide instead of PABA so that their normal growth is stalled. The bacteria are therefore unable to grow and multiply and the disease is thus cured.

In general, it is now known that many human diseases occur either because the enzymes (or biological catalysts)

within the pathogenic bacteria and viruses that infect our body function *properly*, or because our own enzymes within the body function *improperly*. To cure the former we have to design substances such as sulphanilamide that specifically inhibit enzymes of our enemies, the disease-producing bacteria viruses. To cure the latter we need to discover not only the specific enzyme whose malfunction causes the disease but also to find a substitute for it.

Many malfunctioning enzymes within our bodies arise due to genetic causes. A score of diseases such as sickle cell anaemia have already been known to arise from the manufacture of abnormal molecules in place of active enzyme molecules. It is not unlikely that there are hundreds or thousands of such diseases. This is why enzymology with its accent on the molecular basis of human disease is likely to be the keystone of the arch of medicine and pharmacology of the future. Indeed, as Linus Pauling has predicted, one day when our understanding of enzyme activity has advanced sufficiently, many of these diseases will be treated by the use of artificial enzymes specially synthesized to catalyze the biochemical reactions within the diseased body which its malformed enzymes fail to sponsor or support.

9 *New Pathways in Medicine*

The microbiological discoveries of the past three decades are now beginning to usher in a new era of precision in drug research. Far from being a product of the drug industry's traditional method—endless random screening in search of a compound that happens to work for reasons researchers barely comprehend—new drugs will now emerge from an exquisitely detailed understanding of the biological processes of the human body.

The key to this understanding is the fact that body cells are constantly 'talking' to each other through the chemicals they make. Since microbiologists have now begun to decipher the cellular lingo, it is possible to identify the disease-causing compound and prevent the chemical messenger from delivering it. Researchers can thus target their drug in a single highly specific way. A case in point is Smith Kline's recent discovery of a new pill called Tagamet, that cures ulcer almost instantly. It turns off the stomach acid that causes ulcer just like closing a flowing tap. The pain ceases within hours and often the ulcer heals within two weeks.

Tagamet's discovery is the outcome of a decade-long research based on Sir James Black's surmise that the body must contain a second set of biological receptors besides the ones involved in the allergy. Blocking that second set,

Black reasoned, would prevent the stomach from making acid and allow the ulcers to heal. The first two substances he tried did not work, but the third did.

Black's success has shown that many other diseases might be cured by the same strategy based on the biological concept of 'receptor sites' on cells where chemical messages in the body are delivered. This approach is now being tried by Squibb's research team to make an anti-high-blood-pressure drug called Capoten. Capoten researchers aim at interfering with a much more complex biological mechanism of the body than James Black had tackled. Proceeding on the basis of an all but abandoned theory about the relationship between kidney function and blood pressure, they discovered that a drop in blood pressure triggers the kidneys to release renin into the blood stream, where it combines with a protein made in the liver to form another protein called angiotension 1.

By itself this substance doesn't do much. But when slightly modified by an enzyme—a biological catalyst—produced by the lungs, it turns into angiotension 2, a powerful agent that immediately raises blood pressure, first by promptly constricting the blood vessels, forcing blood to squeeze through a narrower channel, and then by signalling the adrenal glands to secrete a hormone that makes the body retain salt and water, increasing the volume of blood to be pumped through the already narrowed vessels.

In hypertension this intricate mechanism fails to shut down when no longer needed. It is but natural then to enquire whether it is possible to switch it off by intercepting the enzyme from the lungs before it acts in the way it does. In other words, while Tagamet blocks a chemical messenger from delivering its destructive message to the stomach cells, Capoten attempts to prevent the messenger from

starting in the first place.

The way to do so was suggested by a lucky coincidence that brought to convergence the work of investigators as far apart as Brazil and Britain. It led to the discovery that something in the venom of an extremely poisonous Brazilian pit viper could stop the lung enzyme from doing its mischief. But when the substance was identified and purified, it was found that only a millionth of a gram could be extracted from a gram of scarce venom. Moreover, it could not be absorbed orally and had to be injected. The way round this dead-end was found by an ingenious inversion of Black's technique. Black had begun with the messenger chemical he wanted to intercept, then altered it until he found a variation that could get to the receptor site first and block it without delivering a message. Since the chemical Squibb researchers had as their starting point, namely, the viper venom extract, breaks down in the digestive tract, any variation of it would do likewise. They had thus to come from the other direction. Taking their cue from an informed guess about the shape of the receptor, which no one had ever seen, they built a new substance to fit into it. So successful were they that the culprit lung enzyme is 10,000 times more likely to hook up with Capoten and be inactivated than to angiotension 1 and turn it into angiotension 2.

Capoten bids fair to revolutionize hypertension therapy. It could—with some luck—replace the currently used beta blockers to prevent heart attacks. For Capoten often makes patients feel good, while beta blockers make them feel miserable enough to discontinue the treatment. This is not to say that Capoten has no problems of its own. It has still to overcome some that usually confront almost all exciting new drugs. Even Tagamet, the modern wonder

drug, is no exception to this rule.

A series of articles in British medical journals has suggested that long-term use of Tagamet could create conditions in the stomach that theoretically might lead to cancer. Smith Kline, its manufacturer, of course, categorically rejects the assertion—a rejection that some distinguished cancer reasearchers at the National Cancer Institute endorse. But only time will tell what its long-term effects are likely to be. Meanwhile, since people with ulcers feel awful, they will continue to stampede for it because it stops the pain instantly.

Simpler versions of the sophisticated techniques of drug delivery that have yielded new drugs such as Tagamet and Capoten are also being employed to reduce the side-effects of older drugs by recourse to new tricks of administering them. What is new is not the drug but its delivery system. Take, for instance, nitroglycerin, a drug used against heart pain. When taken orally, it gives rise to nasty side-effects. High doses have to be given to ensure that it survives passing through the stomach and gets into the bloodstream. However, if it is diffused through the skin, the drug reaches the blood stream directly so that much lower doses can be given, minimizing the side-effects.

This could be done by packing it into a plaster that is stuck on the surface of the skin. The drug diffuses at a constant rate through the skin. Unfortunately, such skin diffusion systems work only for a few chemicals—those consisting of molecules small enough to get through the skin pores. So drug companies are also developing slow release drugs that can be taken orally. Italy's Pharmatec, to cite an instance, has devised its so-called Sure-Cap technology that relies on simple diffusion. A solid drug is enclosed in a semi-permeable capsule which, once swallowed, allows water to seep in. The water dissolves the drug

which then diffuses out into the intestine.

Another device called Oros acts like a miniature pump. Again, a solid core of drug is enclosed in a semipermeable membrane. However, although the membrane permits watery substances to enter, it does not allow the drug to diffuse through it. When gastric juices enter and dissolve the solid drug, this creates an internal pressure which pushes the drug out of a small hole drilled in the surface of the membrane.

Potentially even more exciting than slow-release systems are ones that could target drugs specifically to diseased tissues. They depend on the body's own red blood cells and synthetic fat sacs, called liposomes, to target drugs. Both these carriers tend to converge on the liver. They have therefore been loaded with drugs or enzymes that cure various liver disorders. More extensive applications of these carriers may now become possible.

Dr Gregory Gregoriadis from Northwick Park Hospital in London claims to have devised a system that will permit liposomes to travel to other tissues. He has shown that, if the liposomes are made very tiny, the liver will not grab them and the sacs may remain in the bloodstream for as long as 32 hours. Since the walls of the blood vessels surrounding a diseased tissue are usually damaged and leaky, the tiny sacs can readily enter the diseased organ. If his system works, it may be possible to use liposomes to prime the body's immune system.

The Old Age Syndrome 10

In a famous passage in *As You Like It*, Shakespeare described the seven ages of man beginning with the 'mewing and puking' infant and ending with his 'second childishness and mere oblivion sans teeth, sans eyes' et al. Had the findings of modern biology been known in his day he would have, no doubt, substituted conception for the first stage whereby the individual begins life as a single cell formed by the fusion of paternal sperm and maternal ovum. It is this infinitesimal bit of paternal body that grows to enormous size to make the offspring. It does so by continual replication of the primeval cell, the fertilized ovum. This property of the human cell to continually replicate itself by successive doubling governs the growth of the embryo during gestation and of the baby after birth.

Even when the baby is fully grown the process of cell growth and decay never ceases. Old cells of his body (with a few exceptions) die and new ones, the descendents of old, arise. As a result he is never the same assembly of cells any more than a river is that of the same drops of water. But unlike river drops the descendent new cells are not precisely identical with their dead ancestors. They are 'older' in a sense that I will presently explain. This is why the new cells make the individual older—the ageing

being expressed not by the time interval since the birth of individual cells but by the lineal generation to which they belong.

It is now known that a typical human cell is capable of producing about 50 generations of descendent cells before it loses the ability to function and replicate itself. A descendent cell will even 'remember' its lineage—whether it is a fifth generation descendent or fifteenth. It shows such memory in experiments performed with cultured cells from a human embryo kept in hibernation at sub-zero temperatures in liquid nitrogen. If they are frozen at, say, the fifth replication and then thawed they will undergo 45 more replications and stop. If they are frozen at the 15th replication, they will undergo after thawing only 35 more replications. No matter at what stage of replication they are frozen, the sum of replications undergone before and after freeze is always 50. It is as though the cells have a memory that remember the lineal generation to which they belong when frozen. One such cell is reported to have retained the memory of its lineal descent even after more than 13 year's freeze in liquid nitrogen!

This clocking mechanism in the cell that counts its lineage is virtually a measure of its age. Such ageing of the cells of an individual may well be the explanation for the observed loss of his functional capacity after age 30 years, now estimated at about 0.8 per cent per year. This observation is only a refinement of an earlier discovery made by the English actuary, Benjamin Gompertz, as long ago as 1825. He found that the likelihood of dying doubles every eight years after 30.

Much of modern biological research is a search of the causes of this natural decline in functional capacity of cells and organs in order to discover whether or not it is possible to avert it, if not actually reverse it. The current

consensus is that it is not possible to extend the finite lifetime of normal human cells and their limited capacity to reproduce beyond about 50 lineal generations. But it is possible to transform cultured human cell strains into an 'immortal' cell line capable of indefinite replication by treating it with some kind of virus. The transformation, however, confers immortality at a stiff price we can hardly afford, because it turns the cells into cancerous ones. One is therefore led to the paradoxical conclusion that for human cells to become eternally reproductive or immortal and the individual to escape old age, they must acquire some or all the properties of cancer cells.

There is, however, another category of cells that are also immortal. They are the germ cells—the sperm and ovum. But neither is capable of initiating life by itself. Only when they are fused do they produce the normal (somatic) human cell that grows later into the offspring. But their fusion produces mortality and ageing. So far as one can see at present there seems no way even 'in principle' of extending the lifespan of a normal human cell without making it either pathological like a cancer cell or truncated like a germ cell, the sperm or ovum. We must therefore learn to live with the limited reproductive capacity of normal human cells which is the correlate of human ageing.

The clocking mechanism in the cell that 'records' its lineal descent or 'age' is now known to reside in the cell nucleus and not in its outer cytoplasm, the membrane-bound mass surrounding the nucleus. Since the cell nucleus is the repository of genetic material, it is likely that this clocking mechanism is also of genetic origin. For, if all the complexities of development from conception to sexual maturation are orchestrated by the genetic apparatus, age changes are also likely to be controlled by the

genes as well. No one yet knows how the genes control ageing. But a few informed guesses have been made. One such guess attributes ageing to accumulating errors in the information processing system, represented by the transcription and translation of the genetic message in DNA into RNA and into enzymes and other protein molecules that mediate the body's metabolic processes and thereby lead to a steady decline in the functional abilities of the cell, as well as the metabolic processes of the body. The situation would be analogous to an error in the instruction of an automatic machine tool; the tool would turn out faulty parts which when assembled produce a defective or even a non-functional final product.

Another guess is that age changes are merely a continuation of the normal genetic signals regulating the development of an individual from the moment of conception until his sexual maturation. There may well be even 'ageing genes' that slow or shut down biochemical pathways in a sequential manner and lead to the predictable expression of what are recognized as age changes such as graying of the hair, double chin, wrinkled face, baldness, menopause, diminished hearing acuity, dimmed eye vision, etc. None of these signs of ageing is by itself regarded as a disease even though all of them in their totality do make the syndrome called old age. If so, Lenin was right to castigate old age as the worst disease of mankind. For no advance in medicine will enable one to escape it as one may escape smallpox, cholera, or hopefully some day even cancer. Indeed, if all the major causes of death today were eliminated, death through old age would still occur at 90 or 100 years. Some geneticists therefore think that death of the individual is the genes' way of ensuring their own survival. For by removing worn out individuals, death allows potentially more successful combinations of

genes to supplant them. This is the basis for the tongue-in-cheek grouse sometime made that it is mighty selfish of our genes to make us, poor mortals, mere instruments of their lust for an eternity of life. For under the scheme of things ordained by that god of biologists called Natural Selection, men may come and go but the genes go on forever!

Interfering with Cancer 11

Cancer in man is a group of over 100 related diseases that may arise in any of the body's tissues, and are characterized by the uncontrolled and runaway multiplication of abnormal cells. A substance that can check this prolific growth of cells and thereby either cure the cancer or mitigate its advance was discovered by Alick Issacs and Jean Lindemann at the National Institute for Medical Research in England over 20 years ago. Because it seems to interfere with the growth of cancerous cells, it has hopefully been called *interferon.*

Interferon is the generic name for a class of small proteins secreted by virus-infected animal cells, that act on nearby uninfected cells to render them resistant to a broad spectrum of viruses. Although interferon is not specific to any particular virus, it exerts its protective effect on cells of the same species of animal that manufactured it. Thus interferon produced by rat cells is nearly useless for rabbits, and monkey interferon gives little protection to humans. It does, however, inhibit the growth of a range of viruses, and not merely the virus that stimulated its production. But the inhibition it brings about is indirect : a cell invaded by a virus produces interferon; this causes other cells to produce still another protein, which in turn hinders the production of the virus. It is

this capacity of interferon to hamper viral growth that has been availed of in experimental trials to cure cancer.

Since its discovery over two decades ago, evidence has steadily accumulated to show that interferon plays important roles in the body's complex defencive reactions against viruses as well as cancer cells. It seems to do so by retarding the division of tumour cells, enhancing the expression on tumour cells of cell-surface antigens (foreign proteins that induce the immune response) and either activating or inhibiting B lymphocytes and natural killer cells, two classes of white blood cells participating in immunological reactions. Since all these effects are potentially useful in the treatment of cancer, there has been increasing interest in the possibility of its use for that purpose. But its use in clinical trials has hitherto been greatly hampered by the extreme scarcity and enormous cost of human interferon. The recent advances in the production and purification of human interferon have markedly improved its availability. It is this relatively easier availability of the drug that has now prompted the American Cancer Society to embark on a major investigation of the antitumour effects of interferon on as many as 120 patients. Similar clinical research projects are also getting under way in Europe and Japan.

The most important aspect of interferon treatment is that it represents a new approach to cancer chemotherapy. Whereas conventional anticancer drugs work by being more toxic to cancer cells than they are to normal cells (and hence often have severe side effects), interferon seems to work by inhibiting the division of tumour cells or by enhancing the immune response of the host. Since interferon is a natural substance manufactured by the body's own cells, it may prove effective longer than other anticancer drugs before serious toxic side effects appear.

Even in the unlikely event of interferon having only weak effects on tumour growth, its complete lack of toxicity seems to assure it a high therapeutic index and make it an attractive form of cancer therapy, particularly in combination with other modalities of treatment. The clinical findings to date have been sufficiently promising to inspire not only a massive research effort to prove its efficacy, but also new drives to improve its production to meet the increasing demand.

12 *A New Diagnostic Tool*

Medicine is an ancient art which is rapidly turning into a science, thanks to new diagnostic tools based on discoveries made by physical scientists. A case in point is the discovery of X-ray by the German physicist, Wilhem Conrad Röntgen in 1895. Within a few months of their discovery, X-rays began to be used by doctors to see the insides of their patients from the outside.

What an X-ray plate shows is a still picture of the organ or object viewed. A new deveopment that will produce what is virtually a motion picture or 'action film' of how organs in the body function is now in the offing. The 'film' is designed to provide a detailed chemical analysis which will identify the diseased tissue or organ and give the physician useful clues to match its abnormal chemistry with appropriate drugs.

How can we film the working of an organ *in vivo*? The answer is that it can be done by resort to a new super-sophisticated technique called nuclear magnetic resonance (NMR) spectroscopy.

NMR spectroscopy is one of a variety of spectroscopic methods employed by chemists to determine the molecular structure of complex compounds. It derives its great power from the fact that such a spectrum obtained from a small sample of a complex compound can be used to

identify important groups of atoms within complex molecules—these are the so-called functional groups, such as OH, COOH, CO, etc. The chemists can then piece these groups together one by one, as in a jigsaw puzzle, using supplementary clues from the spectra, and so determine the structure of unknown compounds. Chemists have routinely used the technique for the past two decades to investigate vast numbers of chemical compounds.

Modern equipment and mathematical techniques may soon make it possible to analyze small regions of the human body in the same way as if they were neat handy test tubes without so much as touching the skin, and without any risk to the patient. The aim of the new effort is a quantum leap beyond X-ray scanning—not merely to exhibit diseased areas and organs but to also reveal their actual biochemistry *in vivo*.

The basic idea underlying NMR spectroscopy is the fact that the atomic nucleus of some atoms such as hydrogen and carbon-13 behaves like a bar magnet which spins about an axis. Accordingly, when it spins in an external magnetic field it experiences a twisting force or torque.

This force tends to align the nuclear 'magnet' with the magnetic field, and causes the nucleus to precess. That is, the spin axis itself rotates about the magnetic field direction exactly like a top spinning in the Earth's gravitational field. As is well known, when a spinning top is slightly disturbed, its axis 'precesses' or wobbles round the vertical so that it traces out a cone.

A global scaling up of the same phenomenon is the precession of the Earth's axis around which it performs its diurnal rotation in the gravitational field of the moon and sun. The precession of the axis of the spinning nuclear 'magnet' (that is, the atomic nucleus) about the magnetic field line whereby it describes a miniscule cone

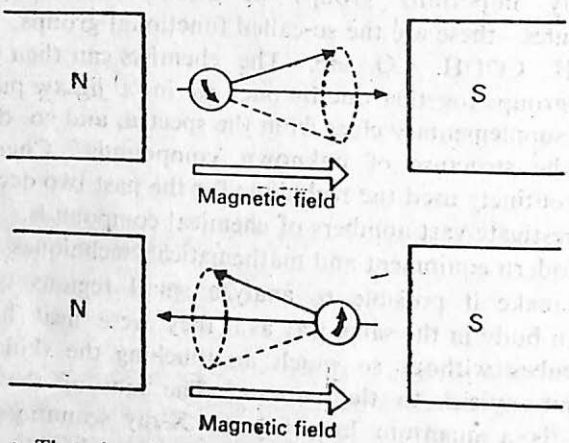


Fig. 1 : The spin axis of a nucleus with spin $\frac{1}{2}$ rotates in a magnetic field in one of two orientations. The state aligned with the field (top) has the lower energy.

as shown in Fig. 1 is merely a micro miniaturization on the atomic scale of a similar wobbling of the axis of a spinning top or of our own earth.

The precessional frequency of the nuclear 'spinning top' is called Larmor frequency and depends on both the spin of the nucleus and the strength of the external magnetic field. For example, for the proton or hydrogen nucleus and carbon-13 nucleus there are two possible alignments; the nuclei line up either with the external magnetic field or against it as shown in Fig. 1. The former state of alignment has less energy and is therefore more likely to occur. Accordingly once the spins are in equilibrium, the majority of nuclei point in the field direction. However, they do not remain aligned in the same way all the time. The spins may be 'flipped' if they happen to absorb a photon of electromagnetic radiation at radio frequency.

This absorption by the 'nuclear spin system' in the presence of an external magnetic field is known as nuclear magnetic resonance (NMR). The equipment devised to secure NMR uses radio waves to stimulate transitions between 'spin states' of nuclei in a magnetic field. In medical applications it is the spin states of the nucleus that are studied. The wavelengths of the radio waves absorbed and the time taken for the nucleus to return to its original state (its relaxation time), provide detailed information about the material, such as diffusion, flow rates, water content, etc. NMR spectroscopy is thus a form of microscopy without a microscope! It provides chemists and physicians with a novel type of artificial vision whereby one can perceive—though not precisely 'see'—the very nuclei of atoms jostling and reacting with one another in complex compounds and materials in the human body.

NMR is important for two reasons. First, it is not likely to carry the same risks of permanent tissue damage as other diagnostic techniques such as X-ray scanning. Accordingly, it may be possible to use NMR techniques when the risks associated with X-ray scanning are just too great; with pregnant women, for example. Secondly, NMR is also likely to provide information not obtainable by means of X-rays because it is measuring different parameters. As already mentioned, it gives an indication of the way organs function *in vivo* rather than the static physical structure shown by X-rays. This is why multinationals such as EMI, Pfizer and Philips are already working on equipment suitable for NMR scanning. EMI hopes to market it very soon.

What is Feedback ? 13

Feedback in a system, whether animal or machine, is essentially a way whereby the output of the system is used to control its working so that it may achieve its desired goal. A case in point is the steam steering engine that turns the ship's rudder. It keeps the ship automatically on a fixed course, come wave, wind, gust or gale. There is nothing mysterious in this type of self-steering mechanism. For it operates in exactly the same manner as the erstwhile helmsman that it displaced. As is well known, the helmsman at the ship's wheel estimates by means of a compass the deviation between the ship's actual and desired course and uses this information to turn the wheel to the precise extent required to correct the deviation. In precisely the same way the ship's servomechanism uses signals reporting the deviation or angular difference between the actual and prescribed course to modify the output of the engine activating the rudder exactly to the extent required to rectify the reported error. In other words, the output of the steering engine is made to influence its input so as to steer the ship automatically on its prescribed course. This feature, whereby the output of a system is used to control the source of its driving power in such a way that power is throttled, if its output rises beyond a determined point, but is amplified, if the

output lags, so that the system regulates itself automatically at the prescribed level, is the heart of all control spstems simulating purposeful behaviour.

This phenomeon is called 'feedback' by communication engineers ; 'servo system', 'closed-loop' or 'closed cycle control system' by systems engineers ; 'homeostasis' by physiologists ; 'reflex neural circuit' by neurologists ; '*petitio principil*' by logicians ; 'vicious circle' by psychologists, and 'boom and slump cycle' by economists. It appears even as the first act of creation in the following metaphysical limerick :

Said a fisherman at Nice
"The way we began was like thees
A long way indeed back
In chaos rode Feedback
And Adam and Eve had a piece."

Its underlying rationale is that life itself originated by recourse to natural feedback (homeostasis) whereby any live organism maintains the constancy of its internal environment, despite random disturbances from within and without. Accordingly such physiological processes as nature devised to help keep constant our body temperature, blood pressure, or glucose concentration in the blood stream are as good examples of feedback principle in action as those contrived by us, such as a thermostat controlling a furnace to steady the room temperature, a computer guiding a missile to its zigzagging quarry in the sky, or a servo steer navigating a ship on its prescribed course. In all these cases feedback, whether natural or contrived, adapts the behaviour of the system to its desired goals by using incoming error-reporting signals to correct the error.

Although a powerful tool in the design of control systems, the feedback principle is not without a serious

pitfall in that systems based thereon are often liable to uncontrolled oscillations or *hunting*. Consider the case of a ship's servo steer itself. Because of the inevitable time lag between the arrival of the signal and the completion of the rectifying action it initiates, it is quite likely that by the time the ship's rudder reaches the desired alignment it has acquired sufficient momentum to overshoot the mark. The error then is reversed and the steering system applies the correction, but because of the time lag it may overshoot again in the opposite direction. A system liable to overshoots of this kind behaves in one of two ways. Either the amplitude of each overgo progressively diminishes and tends to die out, thereby settling the system into a stable state, or it goes on increasing, throwing the system off balance in a frenzy of violent yawing. It is the latter eventuality that often comes to pass, unless the system is cured of it by minimizing the time lags as well as dissipating the system's surplus momentum by means of some kind of braking or damping device.

In general, there has to be quite a precise tie-up between the output response of a servo system and its error-reporting input signals, as will be seen from Fig. 1 representing the essential elements of all such systems employing feedback. The servo's own input x_1 is modified

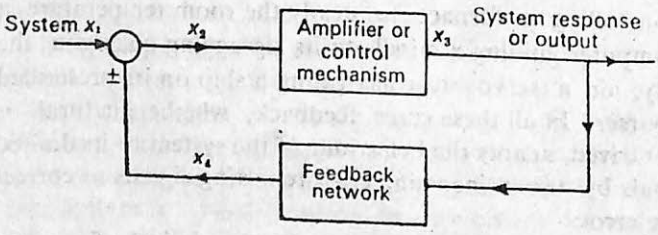


Fig. 1 : Feedback mechanism.

into x_2 by the receipt of error-reporting feedback signal x_4 by addition or subtraction as shown in the equation

$$x_2 = x_1 \pm x_4$$

The resultant signal x_2 is the actuator of the system yielding the output or response x_3 which in turn determines x_4, thus completing the feedback circuit. If for any reason the error reporting incoming signal x_4 fails to modify its own input x_1 to the precise extent required to ensure its stability, it may spark an orgy of uncontrolled oscillations that makes the system utterly useless for any self-regulation. The phenomenon of 'intention tremor' wherein the patient's hand merely ends in violent to-and-fro swings in a vain attempt to pick up a cigarette is a case in point of such a failure of feedback due to an injury in the cerebellum.

There are many situations where even a relatively minor mismatch between the incoming error-reporting signal and the error-correcting output becomes amplified and generates more general disruption and instability if the right action is not taken in time. Feedback theory and cybernetic analysis have led to a better understanding of such problems and how they may be resolved. One outcome of this understanding is the recent world-wide proliferation of satellites in the sky, robots in industry and computers in banks and bureaus. The successes of *contrived* feedback have tempted some enthusiasts to suggest a way of securing an equally spectacular breakthrough in the art of healing our ailing bodies by recourse to its biological counterpart they call 'biofeedback'.

Unfortunately, our understanding of biofeedback, that keeps our body ticking is still very feeble and fragmentary. We have as yet no clue to what W.B. Cannon called the wisdom of the body whereby our internal organs such as the

heart, liver, stomach, kidneys, etc. are able to maintain a relatively stable state of *dynamic* equilibrium that is also a state of healthy well being. It is fortunate that they do so 'involuntarily', that is, independently of our will and consciousness. For if we had to exert voluntary control over, for example, the stomach, we would have to stop doing everything else after a meal in order to supervise its digestive processes. But while it is clearly a great convenience for us that our internal organs look after themselves in our day-to-day lives, there are occasions when the ability to control them would be extremely welcome. The man with a hangover or the seasick traveller would naturally love to be able to quieten his groaning innards!

The general notion that bodily activities can be divided into those that are voluntary and those that are involuntary has a long history. Two thousand years ago, Plato drew a distinction between the superior rational soul in the head above and the inferior souls in the body below. A more modern version of Plato's doctrine is that voluntary behaviour is possible only for skeletal responses produced by the cerebro-spinal system, whereas involuntary behaviour characterizes the visceral and emotional responses of the more primitive autonomic nervous system. This simple distinction held sway for a very long time among philosophers, psychologists and physiologists, as it still continues to do. But the existence of several intriguing examples of voluntary control over apparently 'involuntary' responses has prompted some scientists to suggest that this view may be oversimplified. Hans and Michael Eysensk mention in their book, *Mindwatching*, a famous memory man they call S. He had an exceptional capacity to imagine vividly, which he used to control his heartbeat and temperature. By merely visualizing himself as asleep

or vigorously active, he was able to alter his heart rate abruptly over a range of nearly 40 beats per minute (the average beat per minute is 72). Even more dramatically, he could raise the skin temperature of his right hand by imagining that it was on a hot stove, while at the same time lowering that of his left hand by imagining that it was holding an ice cube.

Still more amazing claims have been made about the powers of Indian yogis, including the ability to make their hearts stop beating! It is difficult to evaluate most of these claims and many yogis are undoubtedly charlatans anxious only to cheat the gullible. But there are exceptions to this general rule. In a serious scientific bid to sort the chaff from the grain, Doctor Bal K. Anand, the Chairman of the Department of Physiology at the All-India Institute of Medical Sciences in New Delhi, tested over 400 yogis under carefully controlled laboratory conditions. Though most of them proved disappointing, a handful did demonstrate unusual abilities. One yogi was able to reduce his heartbeat to half the normal rate by blocking the action of the so-called cardiac pacemaker, and another yogi could make his forehead break out in perspiration without moving a muscle. Two more yogis were able to slow down their metabolism until they were functioning at less than half their normal walking metabolic rate—approximately *five* times as great a drop in metabolic rate as occurs in very deep sleep.

These exceptional cases of control over 'involuntary' activities of the body led the distinguished American psychologist, Neal Miller, to perform an experiment designed to show that what is exceptional could be made normal. Miller experimented with rats injected with curare, a drug which causes virtually complete paralysis of the skeletal muscles involved in breathing, but which

permits the internal organs to function fairly normally. These curarised rats were then subjected to a complicated system to provide them with information (biofeedback) about the functioning of their other organs by a series of rewards and reinforcements experiments psychologists use to teach animals new tricks. Miller claimed that it was possible to make curarized rats learn to increase or decrease intestinal contractions, the amount of blood in the stomach and even control the rate of urine formation. These experiments are the slender basis of the tall claim that man can control his internal organs by an analogous process of 'biofeedback', thus opening up new vistas for the treatment of a wide range of complaints from migraine headaches and hypertension to heart irregularities.

The biofeedback cure stemming from Miller's work with curarized rats simply refers to a technique in which biophysiological instruments provide the patient with information about changes in body functioning of which he is usually unaware. The patient's 'reward' is to observe his increasing control over the working of a part of his own body, and the apparatus is set so as to gradually mould the visceral response in the desired direction. But so far this biofeedback technique has not redeemed any of the promises of its salesmen. Nor is it likely that it will for two reasons. First, Miller discovered that curarized rats showed much better visceral learning than undrugged ones and speculated that curare helped eliminate the various sources of distraction that interfere with learning. So if human patients also need to be paralyzed for biofeedback cure to work properly, the cure is worse than the disease! Second, the putative cure is in any case phoney. For the error-reporting signals that organs receive and the rectifying action they take are conveyed in very complicated codes (like the genetic code still to be

fully deciphered) which our conscious self is unable to decode. Even if it could, it would not be able to communicate the rectifying message in a language intelligible to the organ.

The mere fact that feedback mechanism works both in men and machines is no warrant for assuming that both work in the *same* way any more than for treating birds and airplanes as like mechanisms simply because both manage to fly. Despite the obvious semantic trap lurking beneath the argument based on the feedback principle, it seems to have lured enthusiasts like Miller to push to extreme what is nothing more than a verbal analogy. Merely because *contrived* feedback of automata of our making has been so successful is no reason why its *natural* counterpart 'biofeedback' should have equal success in healing our ailing bodies.

14 *The Fight or Flight Reaction*

The renowned American physiologist, Walter Bradford Cannon, described in his classic work, *The Wisdom of the Body*, what he called the 'fight or flight' reaction. The reaction is early man's instinctive response to a crisis situation he often faced, such as confrontation with a wild animal or a human foe. It supercharges the human body to produce the spurt of physical energy required anyhow, no matter whether he decides to fight or fly his foe.

The stressful situation the encounter causes produces in the human body a large increase in the secretion into the blood stream of catecholamines—adrenaline and noradrenaline. These chemicals are produced by the medulla of the adrenal glands, and at the nerve endings of the sympathetic nervous system. This sets in train a whole series of secondary reactions, and in general, has the effect of increasing all the catabolic activities and mechanisms of the body, that is, those processes which are concerned with the expenditure of energy, and with preparing tissues and organs for physical activity. The heart beats faster. The blood pressure shoots up. The fine air tubes in the lungs dilate to facilitate increased respiratory effort. Blood flow is diverted from the skin and the gut to the muscles. Blood fat and sugar levels are raised. The cortex of the adrenal glands secrete more corticosteroids. The kidneys

secrete more rexin which is one of the factors involved in sustaining a high blood pressure. There is a fall in the level of fibrinolysins in the blood, and as a result clots in the bloodstream form more readily.

All these and other physiological changes in the body are spurs to Cannon's 'fight or flight' reaction. They enable the body to produce the bout of physical effort required to face the stressful situation that starts the reaction. During the aeons of biological evolution the wisdom of the body fashioned an ideal response to the crisis situation often encountered by man in the wild state of nature. Since the crisis was rapidly resolved one way or the other, the stimulus to the emergency reaction was always brief, and the individual—if he survived the encounter—became normal soon after the burst of physical activity initiated by the powerful biological material produced in the body.

But this ideal response of the body to the crisis situations of wild old days of palaeolithic man is not appropriate any more. And yet the crisis situations civilized man faces today do trigger the 'fight or flight' reaction in the same old way, even though the nature of the crises of today is no longer the same. In the first place they are no longer brief and tend to be sustained like the protracted agony of Shah Commission and the like. Secondly they cannot be resolved by a mere surge of physical activity. The result is that continuing stress caused by a contemporary crisis distorts the biochemistry of the body in a vicious way whereby the abnormal conditions of themselves constitute additional stress and engender further aberrations. Homoeostatis—the maintenance of the equilibrium of the internal environment—is irretrievably lost. It is this breakdown in homoeostatis due to prolonged emotional stress caused by long lasting crises of

personal life of today that is now believed to be a major precipitating factor in the incidence of coronary heart disease (CHD).

If so, the question arises whether CHD is really a true disease like rabies or cholera or whether it is merely the natural (though now pernicious) outcome of an individual's physiological reactions to stressful situations of our civilized society. We have hitherto regarded it as a disease to be cured by 'drugs'. Recent evidence seems to show that it is not a true disease which may be cured by appropriate 'drugs'. This is why chemical treatment of high blood pressure, which predisposes one to heart trouble and strokes, is more often symptom suppression rather than a grass root cure. The real cure is some way of relieving the emotional stress that gives rise to the 'fight or flight' reaction in the first place. One such cure suggested by Dr. Malcolm Carruthers, of the Maudsley Hospital, London, is what he calls 'autogenic training'.

Autogenic training is a highly disciplined form of thought control, which the individual practises upon himself. Unfortunately one cannot learn the technique from books; one has to be taught by experts. Once one has mastered the routine, one can, it seems, switch off that disturbing, destructive, sympathetic nervous system, and bring into play the calming and restorative parasympathetic nerves instead. One can then direct one's mind to the liver, or the stomach, or to troublesome piles, or wherever, and work miracles on recalcitrant cells. Autogenic training is thus a specific and unique form of self-administrated psychotherapy. It is, according to its author, Dr. Carruthers, the 'Western answer to Eastern techniques such as Yoga and Zen meditation'.

Unlike its Eastern counterparts, autogenic training does not rely on esoteric mysticism but on securing a better

communication between two hemispheres of the brain—the rational left and the intuitive right. It seeks to combine left brain rationality and right brain psychic abilities in conjunction with fore-brain governing capacities to pull the mind out of its anxiety-cum-fear syndrome. This rationale may sound scientific. But it does not seem possible to devise a scientific test to validate its claim that it really 'works'. The reason is that any clinical trial that may be devised is not testing something objective such as the efficacy of an antibiotic, but the purely subjective response of an individual to a treatment without drugs. Such a test is incapable of refuting the claim and therefore *not* scientific. For after all it may well be that those who recover are tough minded enough to pull themselves up by their own shoestrings and those who don't are not. In psychotherapy God helps only those who help themselves!

The Human Brain : Single or Double Organ? 15

The body plan of a human being provides for two types of organs. Type I are single organs performing essentially indivisible functions such as blood circulation by the heart or digestion by the stomach. Type II are paired organs performing separable but superposable functions such as breathing, seeing or hearing by two lungs, eyes and ears, respectively. The great neurophysiological enigma of today is whether the human brain is a single (type I) or double (type II) organ.

At first sight it appears to be a single organ controlling the sensory and motor activities of the body: vision, hearing, muscular movement and so on. But recent research seems to suggest that it is a double organ consisting of right and left hemispheres connected by a broad nerve cable and lesser bridges called the corpus callosum (see Fig. 1). As will be observed, each hemisphere is a mirror image of the other and is mainly associated with one side of the body: the right hemisphere controlling the left and the left hemisphere the right.

It is true that this broad division of sovereignty over the body between the two hemispheres is not absolute. In cases of brain injury when an area in one hemisphere is damaged, the corresponding area in the other can often take over its work and so control the functions involved

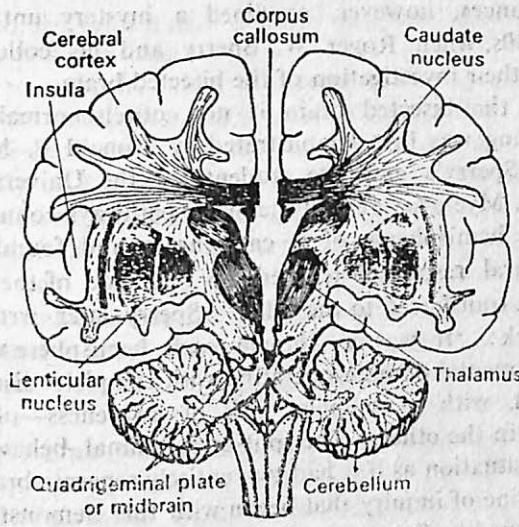


Fig. 1 : Vertical section of a human brain.

for both sides of the body. But when the connecting corpus callosum linking the two halves is surgically removed, each hemisphere functions independently as if it were a complete brain. There then emerge in the cranium two separate independent spheres of consciousness!

The possibility of exploring the separate functions of the two hemispheres was originally suggested by the experience of neurosurgeons who had made a surprising discovery. They discovered that in cases of severe epilepsy the disease could be greatly mitigated by surgically removing all of corpus callosum linking the two hemispheres. This severance helped to prevent the spread of epileptic seizures from one hemisphere to the other. The operation proved so successful that beginning in the late 1930s it became an accepted treatment of severe epilepsy. The seeming irrelevence of the corpus callosum in such

circumstances, however, remained a mystery until the early 1950s, when Roger W. Sperry and his colleagues took up their investigation of the bisected brain.

That the bisected brain is not entirely normal in its functioning was first demonstrated by Ronald E. Myers, one of Sperry's graduate students at the University of Chicago. Myers severed all the major pathways connecting the two hemispheres of a cat's brain and found that behavioural responses learned by one side of the brain were not transferred to the other. Sperry later wrote of this work: 'It was as though each hemisphere were a separate mental domain operating with complete disregard —indeed, with a complete lack of awareness—of what went on in the other. The split-brain animal behaved in the test situation as if it had two entirely separate brains.'

The line of inquiry that began with this demonstration was pursued by Sperry and his co-workers through a wide-ranging series of animal studies, designed to analyze the separate organization and operation of the brain's hemispheres. Beginning in the 1960s the basic experimental techniques worked out in detail with cats, monkeys and chimpanzees were applied to human patients who had undergone the brain-splitting operation for the control of intractable epilepsy. These experiments were done mainly by Sperry for which he was awarded the 1981 Nobel Prize in Physiology.

Although experiments with split-brain patients have shown the virtual independence of both the hemispheres, the right hemisphere is decidedly inferior to the left in certain respects, such as in its overall command of language. The reason is the location of speech centres in the left hemisphere. This is most clearly shown by the fact that when information (visual or tactile) is presented to the dominant left hemisphere of a split-patient, he is

able to deal with it and describe it quite normally both orally and in writing.

For example, when a picture of a spoon is shown in the right visual field or a spoon is placed in the right hand (perceived by the left hemisphere), he is able to readily identify and describe it. In contrast, when the same information is presented to the right hemisphere, it fails to elicit a similar spoken and written response. This debility of the right hemisphere to comprehend language is further corroborated by the fact that although it can respond after a fashion to a concrete noun such as 'pencil', it cannot do as well with verbs. After all verbs are more verbal than nouns.

Split-brain patients are, therefore, unable to respond appropriately to simple printed instructions such as 'smile' or 'frown', when these verbs are flashed to the right hemisphere. Nor can they point to a picture that corresponds to the flashed verb. Such studies also indicate that the right hemisphere has a very poorly developed grammar. It seems incapable of forming even the plural of a given noun, for example, let alone the conjugation of an irregular verb!

In general, then, the command of language by the adult right hemisphere in no way compares with that by the left hemisphere or, for that matter, with the extent of language present in a child's right hemisphere. For it seems from a number of neurological observations of growing children from ages one to four that the right hemisphere is about as proficient in handling language as the left up to age four or so. Moreover, studies of language learning by such children, particularly with respect to grammar, strongly indicate that the foundations of grammar, the bedrock of language, so to speak, are somehow inherent in the human brain and are

fully realized between ages two and three.

The puzzle then is this. While in the young child each hemisphere is about equally developed with respect to language and speech function, this capacity seems to evaporate in the right hemisphere during subsequent maturation. It is difficult, indeed, to imagine an underlying neurological mechanism that permits the establishment of a capacity of high order in a particular hemisphere on a temporary basis.

The obvious implication is that during subsequent maturation of the child, the process and system that sponsor the manifestation of language capacity in early years are somehow inhibited and dismantled in the right hemisphere and allowed to reside only in the dominant left. Yet the right hemisphere is not in all respects inferior or subordinate to the left. Tests have demonstrated that it excels the left in some specialised functions such as visualization of images that defy verbal description.

In short, all the evidence indicates that separation of the hemispheres creates two independent loci of consciousness within an organism. It is a disturbing conclusion for some who view consciousness as an indivisible property of the human brain whose bifurcation opens the door to Jekyll-and-Hyde type of schizophrenia with the difference that the human mind is not seized by one or other alternately but by both at the same time!

It seems premature to others who insist that the capacities revealed so far for the right hemishere are at the level of an automaton. There is, to be sure, hemispheric inequality in the patients examined, but it may well be a characteristic of only the few split-brain individuals who alone have been studied so far. It is quite possible that if a human brain were divided in a newly born baby, both hemispheres could, as a result, separately and

independently develop mental functions of a high order at the level attained only in the left hemisphere of normal individuals. Or, it may damage the child irrevocably and permanently. We just don't know!

Why is a Computer not as Intelligent as a Man? 16

Human intelligence resides in an astonishing information-processing system—the human brain. It is an assembly of an enormous number of components activated by an extremely small amount of energy, with an indefinitely small failure rate and a virtually unlimited memory. To produce a machine mimicking its intelligent behaviour one must enclose ten billion neurons weighing barely a kilo within a litre of volume consuming in all about 10 watts and yet storing a million billion (10^{15}) bits of information in its memory. No way has yet been found to make such a machine with synthetic materials. The closest approach that is also a very wide miss indeed is the modern computer. Though in some respects computer and brain are as closely allied as next of kin, they are in others as far apart as stars and sputniks.

Consider, to start with, their resemblances. They are mainly three. First, the computers can be programmed to make decisions of some sort even as human brains do. Second, both employ feedback whereby they monitor and self-rectify their own aberrations in a changing environment. Third, both treat their environment—internal and external—as a source of 'information' which must somehow be communicated over channels that form an integral part of the network before it is 'processed'.

These three resemblances appeared at first encounter so striking as to earn the computers the nickname 'giant brains'. But we now know better. Alas! the divergences diverge far more radically than the coincidences coincide.

The most conspicuous departure is in respect of methods of storage, recall and processing of information. Because the methods of data storage, access, and processing practised in computer engineering today are very primitive vis-a-vis their infinitely more complex but unknown analogues of the living brain, the computer has not yet come of age to wean itself away from the tutelage of algorisms. That is, it can handle only such tasks as can be performed by a more or less slavish follow-up of prescribed routines. The living brain, on the contrary, operates essentially by non-algorithmic methods bearing little resemblance to the familiar rules of logic and mathematics built into the computer. It is therefore no wonder that the latter is hard put to imitate such other creative feats of the living brain as are not readily amenable to algorithmic routines. All it has been able to do so far is to ape them crudely, and that too by the invention of new kinds of highly sophisticated machine languages or codes that are nowhere like those of the living brain. It seems that the language of the brain is logically much 'simpler' than any we have been able to devise so far. As von Neumann once remarked, we are hardly in a position even to talk about it, much less theorize about it. We have not yet been able to map out the activity of the human brain in sufficient detail to serve as a foothold for such an exercise.

With the failure to make in practice brain models or computers capable of exhibiting human intelligence, computer researchers have been obliged to essay a more modest goal, namely, synthesize some single and severely

limited aspect of human intelligence. After decades of painstaking—often frustrating—research all that they have been able to do is to produce a series of clever computer programmes known as 'expert' systems. These convert a computer from an ignorant slave into an intelligent assistant crammed full of highly specialized knowledge of a particular field, and capable of exhibiting some of the thinking and intuition that human experts use to apply such knowledge. A case in point is the interpretation of some geological data almost as competently as the oil and mining expert whose knowledge they embody. The trick lies in capturing the oil expert's knowledge in a usable form for computer manipulation.

To understand just what is involved let us recall that the computer merely manipulates symbols—combinations of 0 and 1—and it is irrelevant to it whether the particular symbols being processed at any moment represent data, programme instructions, or system software. The data is meaningless without the programme that defines it; the programme meaningless without the data. Neither has meaning without the human knowledge that envelops the system, the programme and the data. Although patient and obedient, the computer is as idiotic as the Casabianca boy who would not leave the burning deck in stupid compliance with his father's instruction not to do so. It cannot therefore function in a contingency not envisaged in the programmed instructions. If it is to act as intelligently as a human being is expected to do, a way must be found to embody *all* of the expert's knowledge in its programmed instructions to enable it to tackle problems without human intervention. It seems that it is not yet possible to do so except in some very narrow areas of specialization, for specialist expertise is easier to assemble than the vast amount of diverse knowledge that human

beings bring to bear on the problems of everyday life. A good example of how to capture the knowledge of a specialist expertise is a programme called Dipmeter Adviser, which interprets geological data from an oil well measurement device called Dipmeter. A typical rule from the programme says: 'If there is a red pattern over a fault, the direction of the red pattern is perpendicular to the fault, and the length of the red pattern is greater than 200 feet, then the fault is a growth fault'. The next rule is: 'If the fault is a growth fault,.....' and so on.

This programme (Dipmeter Adviser) was developed by Schlumberger, a multinational firm, that has a near monopoly of measuring well geology for oil companies in search of oil. To get at the geology of a well, various measuring devices (including dipmeter) are lowered into it on thin wires and data signals sent back to produce a 'log' of the well. Interpreting such logs requires skill normally acquired by long painstaking study. Dipmeter Adviser is an attempt to encapsulate the expert's skill in a master computer programme. It is the result of a prolonged collaboration between computer experts and the Schlumberger's top log-interpreter, Mr. Al Gilreath. It enables interpreters of logs less skilful than Gilreath to draw on his expertise and to reach conclusions that they could not otherwise obtain. In this area of expertise, the computer run on Dipmeter Adviser simulates the 'intelligence' of Mr. Gilreath.

Dipmeter Adviser is only one of the many programmes devised to capture the 'intelligence' of the expert in diverse fields of science and technology. One of the earliest is Dendral which does mass-spectrographic analysis of gases more accurately and conveniently than lab assistants. It is now being used on a time-sharing computer by chemists round the world. Another is MIT's Maesyma

which acts as a mathematician's assistant, manipulating algebraic expressions to save its user's time and effort.

It is not merely industrial and scientific problems that are tackled by these programmes. Researchers have also made programmes designed to simulate intelligence in other areas such as playing games, writing poetry, composing music, recognising patterns and language translation. In all such cases, with one exception, programmers have not had much of a success. The sole exception is playing games such as chess. Even 10 years ago the ability of a machine to play chess at national championship level would have been acclaimed as proof of synthetic 'intelligence' especially because of the miserable performance of most computer chess programmes of the period. Now Belle, the Bell Lab's chess computer can play the game at a level of 2,300 points on the World Chess Federation's rankings. In comparison, Mr. Anatoly Karpov, the world champion, has a rating of 2,700 and the average tournament player has a rating of 1,500. Such amazing programmes have been produced not by any new insight into the working of the living brain but by following the same old trail. That is, by making the computer's plod more plodding by improving its infallible memory, electronic speed, vast computation capablities, and prodigious information-processing prowess.

Why Can't Our Damaged Nervous System Repair Itself? 17

One of the many neurophysiological mysteries puzzling neurophysiologists today is the difference between the nervous systems of lower and higher vertebrates in spite of the basic unity of life. One is regenerate in that it can self-repair an injury while the other can't. Cut the optic nerve of a frog, or the spinal cord of a fish, within weeks the frog will see and the fish will swim again. The same lesions in a man or a mammal will cause irreversible blindness and paraplegia. It therefore seems that as animals ascend the evolutionary ladder, they lose the regenerative capacity of their nervous system. Must man, in common with mammals, accept the loss or can the regenerative capacity of their central nervous system be reawakened?

To answer the question it is necessary to digress a bit on neuron, the basic cell of the nervous system in vertebrates and most invertebrates from the level of anidians. The discovery of neuron or nerve cell as the basic unit of the nervous system was made by the Spanish histologist, Roman Y. Cajal, for which he was awarded the Nobel Prize in 1906. His discovery paved the way for the recognition of the neuron's fundamental role in nervous function and to a modern understanding of the nerve impulse that activates the nervous system.

Neurophysiologists have shown that the material basis of both the wisdom and economy of the animal brain, including our own, is the network of neural communication system. It keeps the organism informed of the states of affairs in its external and internal environment. It can then adapt itself in time to the changing vicissitudes of its habitat for survival in a hostile world notoriously 'red in tooth and claw'. 'To beware one must be aware' has been the leitmotif of life ever since its emergence. During the aeons of its slow climb out of the pre-Cambrian mud and slime it has gradually perfected a mechanism of acquiring awareness of the potentially dangerous or beneficial situations in its surroundings. Such a mechanism is what Sir Charles Sherrington has called the 'enchanted loom' of neurons or nerve cells, whose function is to transmit messages from the sense organs to the central nervous system and from the latter to the muscles and glands. The incoming or 'afferant' messages are decoded and the outgoing or 'efferent' messages framed or coded in the brain and its offshoot, the spinal cord. The nerves merely act as conducting channels between the peripheral outposts of the body and the central nervous system within. The whole purpose of the nervous system is thus to bring afferent neurons into touch with efferent ones, in order to bind one part of the organism to another in such a way that what the environment is doing to the organism at one place may evoke an appropriate response in other parts even though they may be situated elsewhere. Such responses, for example, could be stimulating or restraining movement in the muscles or secretion in the glands. This is why the vital processes of life are the outcome of myriad messages flashed back and forth along the neurons. What then is this wonder stuff of a neuron which is the very warp and woof

of the nervous system of animals and men?

If we observe a neuron with the naked eye, it appears as a long cord of whitish, translucent material. The large nerve trunks such as the sciatic in man may be half an inch in breadth, though the ultimate branches are scarcely visible thin gossamer threads. Under the microscope the gossamer thread is seen to be made up of a number of fibres about one thousandth millimeter in diameter, each of which acts as an independent channel. Consequently a nerve of medium size may contain several thousand fibres of different lengths varying from a few hundredths of a millimeter to a few meters. The reason is that while some are connected to inside glands close at hand, others have to reach the distant sense organs on the outskirts of the body such as eyes, ears, limbs, skin and muscles all the way from top to toe. Consequently there are many kinds of neurons classified variously according to situation, shape, size, number and length of branches, and so on. But despite their diversity, they are basically alike in that they consist of two essential parts, first, the soma or nerve-cell body and, second, its offshoots or branches which are nerve fibres.

Although the soma of a neuron may ramify into one or several branches, one and only one of them is distinguished as the axis cylinder or axon, the others being called dendrites or end feet. What distinguishes the axon from others is that when the neuron itself 'fires' it is the axon that carries the outgoing nerve impulse *away* from the soma. Its other dendrites, on the other hand, convey *towards* the soma the incoming impulses sent by other neurons in its vicinity. Again although a single axon conducts the impulse away from the soma, it can convey it to several other adjacent neurons. The reason is that as we approach its terminal the axon branches freely into

several terminal structures or end bulbs which impinge on the dendrites of other adjacent neurons across some intervening junctional material. This junction is called a synapse (see Fig. 1).

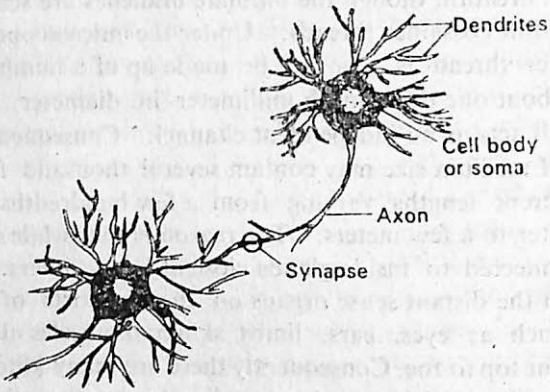


Fig. 1 : A neuron.

The synaptic arrangement by which communication is established between contiguous neurons varies considerably in detail in different situations. But in all the various anatomical arrangements the function of the different types of synapses is fundamentally the same. In each case under certain conditions an electrochemical disturbance or impulse fired in a neuron is carried at a fixed speed along its axon across synapses to the cell bodies or somas of one or more adjoining neurons. In other words, a neuron is a single-lane channel of an axon with one or more outlets into its neighbours delivering to them the impulse it originates. It is by means of the passage of such an impulse along its axon across synapses with other adjacent neurons that it tends to stimulate or inhibit them.

To revert now to the problem of self-repair in the

nervous systems of higher vertebrates, it has not changed materially since the time of Cajal. As early as the 1920s, he had clearly perceived that its two prerequisites were signals for axon growth and signals for axon guidance, both apparently lost at maturity. In this the mammalian nervous system differs not only from the central nervous system of lower vertebrates, but from the mammalian peripheral nervous system too, wherein cut nerves do grow. The reason is the differences between central and peripheral glial cells. Whereas peripheral glia tend to form a tunnel through which a growing axon may extend, central glia at the site of a lesion form an apparently impenetrable scar. This obstacle to regrowth was partially overcome in 1981 by A. Agnayo and his colleagues by grafting sciatic nerve in spinal cord, brain stem and cortex of a rabbit. The grafts were seen to induce sprouting of adult neurons for up to 2 cm, which is probably more than what most central axons ever attain in normal development. The experiment clearly shows that axons can be coaxed to grow. But it has not yet been demonstrated that they can be guided to the appropriate targets so that it remains possible that these factors that drive them to terminal differentiation also blind them for ever to the signals that directed their earlier growth.

To unleash the extension of such undirected axons would, therefore, be to invite consequences far more hideous than paraplegia or blindness the regrowth is meant to cure. Hence the need to know not only what induces the growth of fibres but also what guides them to their targets and determines what they do when they arrive. In our search for this knowledge two facts seem to be relevant. First, in those species in which central nerves regenerate, the neural tissues continue to grow in adult life. The retina of the frog and fish, for example, continue to recruit new

cells indefinitely. Second, animals whose central nervous systems regenerate never make very sophisticated use of them. If a frog's eye is inverted before it is allowed to rejoin to the tectum, the frog never learns to adjust to the rotated image. A man, similarly handicapped, can learn to readapt himself—albeit after some period of initial confusion and discomfort—to seeing objects almost 'normally' even when wearing special lenses which invert everything seen through them. Possibly the loss of developmental plasticity is the price mammals have paid for the synaptic plasticity that enables us to learn. Why such loss should be the concomitant of an increase in synaptic plasticity, however, we shall be unable to guess until we understand learning. In the meantime, we are left with Cajal's verdict of more than half a century ago : '... in adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated. It is for science of the future to change, if possible, this harsh decree'. Neurophysiology has just taken its first faltering footstep in the long march towards its revocation.

Hearing with Eyes, Seeing with Ears 18

In one of his inimitable satires Voltaire describes the chagrin of Micromegas, that intrepid voyager of interstellar space from Sirius to our earth, because in spite of his thousand-odd senses he did not have enough of them to apprehend all that there was in the universe to see and know. He pitied us poor earthlings who had to make do with only five. Would we be better off if we had some more? The answer requires a probe into the anatomy of our five senses of touch, taste, smell, hearing and vision.

If we leave aside vision, the other four senses involve the transport of some material from the object observed to the observer. Such, for instance, is the case when we actually carry our hand to an object to touch it, or our tongue to taste it, or when we smell it by the carriage of material effluvia exhaled by it to our nostrils. Even hearing involves material transport. Although in this case it is only a state of disturbance that is transported from an object to a listener, such a disturbance in turn needs a material medium such as air for its propagation.

Because of the need to transport materials to external objects or to have intervening material media to carry disturbances such as sound waves, in order to produce interactions between them and sentient beings, all such means of apprehending external objects suffer from several

crippling handicaps. To mention only two, the material may remain trapped within the gravitational field of their environment or their motion may be dissipated within a short range like ripples on a lake or a scream in air.

The only sense that is relatively free from these drawbacks is vision because propagation of light on which it depends requires no material medium to carry it. It travels freely through the interstellar void. This is why we can see the sun and stars by the light with which they shine. But the light these celestial objects radiate is not merely the small band of rainbow colours from violet to red that our eyes can see. It extends far beyond with wavelengths both longer and shorter than those of visible light. It begins with red light at one end of the spectrum and continues through infrared to radio waves thousands of metres long. At the other (violet) end it proceeds through ultraviolet down to X-rays and gamma-rays accompanying nuclear changes occurring within stars and galaxies. The reason why our eyes are 'colour blind' to both infrared and ultraviolet radiations is rooted in the behaviour of biological materials of which our eyes are made when exposed to them.

Radiation in the hard ultraviolet, X-ray or gamma-ray bands is very energetic. It carries enough energy to break the chemical bond that holds biological materials together. A biological sensor like our eye would be destroyed if it were designed to absorb such high frequency radiation. It is like a mini bullet piercing through the macromolecule of a retina cell. (Incidentally this is why our atmosphere had to develop an ozone layer to absorb the sun's ultraviolet rays before life could emerge on earth and its possible depletion by various pollutants now is a great hazard.)

On the other hand, low frequency infrared and microwave radiation carries so little energy that it would

be unable to induce the atomic transitions necessary to record detection in a molecular pigment such as rhodospin, the complex organic compound in the retina of the eye. Its impact on the retina is a non-event. The detection waveband of the eye is thus severely circumscribed by the need to record reliably and yet avoid destruction. The waveband of visible light alone conforms to the permissive limits.

Had these findings of modern science been known in his day, Voltaire would have realised that a plethora of extra senses was not necessarily an advantage, nor a lack of them a serious handicap. For any such extra sense that depended on material transport or material media for producing the interaction required to register a phenomenon on the consciousness of an observer would be of no more use than the senses we already have. What is required is a biological sensor that can see 'colours' of light both more 'infra' than infrared and more 'ultra' than ultraviolet. But since no biological sensor can sense the incidence of the former and endure the impact of the latter, what then must we do?

Obviously what we need to apprehend completely the universe around us is not a gift of extra senses but the better use of those we have, so that we may learn to see not only with our eyes but with all our senses, somewhat like Zarathustra teaching his listeners to hear with their eyes. This is precisely what present-day astronomers are attempting to do by devising 'artificial' vision that slips off the biological straitjacket of the human eye. By making apparatus that can record radiation in the complete range of the extended spectrum of both visible and invisible light, in a manner perceptible to some one or other of our five senses, they enable us to 'see' invisible light (cosmic radio waves) with our ears and really teach us how to find a 'higher triumph' in remaining masters of what Nietzche

himself described as the motley whirl of senses. This motley of senses is reduced to order by the wide diversity of apparatus designed to detect all kinds of radiations included in the extended electromagnetic spectrum, from long radio waves through visible light to short cosmic rays.

Since the early 1960s astronomers have been busy constructing such apparatus of great power and precision : radio telescopes, gamma-ray, X-ray, ultraviolet and infrared space probes. The observations they have made in different wavebands with these artificial 'eyes' have each revealed the existence of bizarre and unsuspected celestial objects that were completely invisible to the human eye. Cases in points are quasars, pulsars, radio galaxies, infrared stars, black holes, violent galaxies, black body microwave background radiation, the putative relic of the creation of our universe, and the like. No wonder the astronomers even twenty years ago observed the universe through rose-coloured glasses and built up as unrepresentative picture of its structure as a blind man's identification of an elephant with its trunk.

Psyche and Soma 19

It is an old human intuition that psyche and soma, or mind and body, are one. They are one in the sense that mind of man is all of his being that is not his flesh, bone and brain. This inexplicable connection of ethereal mind and corporeal body that is its habitat, is the core of the mind-body problem that has bedeviled philosophy in the past as viciously as it does today. The problem arises because every man seems to have two distinct aspects. Certain of his qualities and actions belong to him as a physical body that can be objectively observed and can be localized in space. But there are also others within him which are only subjectively experienced and are not obviously connected with any physical organ, as for instance, unspoken thoughts, wishes and feelings. Since these internal activities and processes are not publicly observable and cannot be easily localized, they are thought of as non-physical. It is then a short step to refer them to some nonphysical entity which is their abode as the body is that of observable physical activity. This seat of non-physical processes is called mind (*nous*) or soul (psyche). It is an attractive step taken by almost all ancient philosophies of the world because it leaves open the possibility of life after death. The body obviously perishes, but the mind or soul may survive for ever.

Natural and attractive though the hypothesis of soul or mind is, its underlying dualism bristles with logical difficulties because of the close and inescapable connection between mental and purely bodily functions. Aristotle seems to have been the first to suggest a way out when in his *De Amina* he put forward a theory of the soul as the 'form' of the body—'form' being that shadowy residual that remains after its material content is drained away. But as 'form' so defined is inseparable from the body, it cannot be relied upon to provide a foothold for the immortality of soul. So Aristotle made an exception in favour of intellect (*nous*) which he regarded as separable from the body and therefore capable of survival after death.

This unsatisfactory compromise was in general adopted in the Middle Ages as being in accordance both with the facts of biology and the demands of religion. But the problem became acute in the seventeenth century when the new mechanical wonders of the time—the self-chiming clocks and the hydraulic machines pumping water into the fountains of royal gardens—ushered in an age of mechanistic rationalism. One consequence of the new outlook was Descartes' mind-body duality. He held that body and mind, *res extenso* and *res cogitans* were in their intrinsic natures irreduciably unlike. *Res extenso*, extended substance, subsisted essentially as matter moving mechanically in space and time. *Res cogitans*, thinking substance—essentially mind, but mind without extension—moved in its own way in the activities of desiring, thinking, willing, and the like. Both these substances were poles apart. Nither could have any relation with the other or any effect upon it. But as this separation of mind and body could not be maintained in view of their obvious connection, he begged the problem by invoking God who 'by being the

creator of both extended as well as thinking substances was also able to be the ground of their mutual relationship'.

Descartes' recourse to the *deus ex machina* of God does not solve the problem of mind-body duality. It merely masks the incompatibility of three basic propositions he found himself maintaining: (1) that all physical events are completely explicable in terms of physical laws, (2) that the mind is an entity of a different nature quite disparate from anything physical, and (3) that every mind is in intimate connection with some physical body. Subsequent discussions of the problem have been largely determined by a desire to escape from this impasse. No way has yet been found though the emergence of a new discipline, cybernetics, some four decades ago did spark the hope that discovery of the secret of mind was round the corner. The expectation was natural as cybernetics is a quest for the physical basis of human intelligence, or what we call mind, in order to mimic its activities. It proceeded on the plausible assumption that all the remarkable powers of the living brain stem only from (a) the topological organization of the network of its constituent neurons and (b) the dynamics of neural impulse propagation, without any specifically vitalistic powers which could not be duplicated by man-made devices. In other words, what we call mindlike behaviour of the living brain is wholly a property of the neural material of which it is made, so that we do not require what G. Ryle calls 'a ghost in the machine' to activate it. If so, we should be able to make machines capable of functional duplication of the living brain. No such machine has yet been made. The present-day computer, the nearest analogue of the living brain, resembles it as little as a sputnik does a star. We are not likely to stimulate the living brain till our next

breakthrough into its neurophysiological complexity.

Unfortunately, such a breakthrough is not easy to come by. For there is a kind of indeterminacy which acts as a barrier to our understanding of the living brain. The indeterminacy arises from the fact that the more 'micro' our neurological probe, the less 'macro' is our comprehension of the working of the cerebral cortex as a whole. The way out of this dilemma is a synthesis of both micro and macro approaches. But the desired synthesis is not likely to be a mere derivation of macro or aggregate effects by some sort of statistical averaging of myriads of micro neurological events, as thermodynamics and statistical mechanics are of certain physical phenomena such as the behaviour of gases. The transformation of trillions of nerve impulses, surging back and forth helter-skelter in billions of neural channels into the world of colour and form that we actually perceive and reason about, can hardly be achieved in such a naive fashion. Nor can mental activity, including the emergence of human intelligence, be sheetanchored to a sort of summated upshot of elementary reflexes, those 'atoms of behaviour' whereon incipient psychology tried in vain to rear itself. It can only emerge from an understanding of the logic of the living brain which is very different from that of the cybernetical machines we have hitherto made, to simulate its working, albeit in a rudimentary way.

It seems that the logic of the brain departs in many significant ways from the conventional procedures of mathematics and mathematical logic that are the main inspiration of the construction plan underlying our so-called intelligence machines. To name one specific instance of such departure: the 'logical depth' of our neural operations, that is, the total number of basic operations from (sensory) input to (memory) storage or (motor)

output, seems to be much less than it would be in any artificial automaton dealing with problems of anywhere nearly comparable complexity. This is why it is dangerous to identify the real physical (or biological) world with the models we construct to explain it. The problem of understanding the animal nervous action is much deeper than the problem of understanding the mechanism of any automaton of our making.

Because of our continuing ignorance of logic of the living brain research must be much broader based than is the case now. It is being pursued at present by recourse to the micro approach of neurophysiology, on the one hand, and the macro one of psychology on the other. The hope that two approaches are like boring a tunnel from two sides and will some day meet may well be wishful thinking. Brain research therefore must rear itself not only on the physics, chemistry and biology of nerve cells supplemented by the revelations of psychology, but it must also borrow such insights as linguistics, aesthetics, and the humanities are able to give. For example, Fourniés surmise that human speech is a window on the working of the cerebral cortex may well be truer than we know at present. Moreover, the artist too has long been making meaningful and communicable statements, if not always precise ones, about complex things. In particular, it is well to recall that most of what we know at present about the mind of man is to be learned not from the writings of scientists so much as from those of men of letters—the poets and philosophers, biographers and historians, novelists and literary critics. If the human mind is to uncover its working, it cannot afford to neglect any way of gaining insight. Indeed, it needs like the youthful Bacon, to take 'all knowledge' for its 'province'. For thus alone may we hope to stumble on some enlargement

of the boundaries of natural science able to reveal to us the secret of the human brain's uncanny wisdom. Many scientists are trying to create that enlargement today. But we must not be too impatient if most of them happen to miss rather than hit the target. For after all the secret of the human mind is a primeval mystery. In the words of an ancient epigram:

Though many a thing is unfathomable for mankind,
Nothing looms more ineffable than the mind of man.

On Mimicking Nature 20

Mimicry of nature is nothing new. Men have long dreamt of flying like birds by putting on wings. This is how the mythical engineer craftsman, Daedalus, imprisoned by King Minos in the labyrinth he himself had constructed, is said to have made his escape. The celebrated Leonardo da Vinci gave this mythical idea a more practical slant when he sketched in his famous notebook the design of a flying machine based on the bat's wings.

Four hundred years later the French Engineer, Clement Ader, implemented Leonardo's design by constructing the first man-made machine reputed to have actually flown. But Ader did not try to move the wings as in the natural model. He had observed that the attempts of his predecessors to fly the machine by moving its wings had not succeeded. He realised that the increase in dimensions from those of a bat's wing to a 14-metre wingspan required a different method of propulsion. He used propellers made of quill feathers.

Direct inspiration from nature is always useful though exact imitation may not work as was the case with Ader's flying machine. An example of a direct inspiration that is capable of exact imitation is provided by observing dolphins moving in water. They move at great speed with minimal muscular effort because the peculiar characteristics

of their skin damps out turbulence of water. It suggested the use of synthetic dolphin-like skins for torpedoes to reduce turbulence and achieve greater speed with the same engine power. Likewise, vehicles have been designed by the US Army that substitute legs for wheels, and are directly copied from the articulated legs of certain insects (anthropods) to permit movement in swamps or over very rough terrain.

Despite the usefulness of exact imitation of nature in a few cases, it is often difficult, if not impossible, to copy nature to the dot because of the difference in scale, materials used, and other reasons. The essential point is not to copy in detail but to understand why things work in nature in the way they do.

A generalized search for inspiration from nature may appropriately begin by a study of living beings from several points of view. Animal muscle is an efficient mechanical motor; storage of solar energy in a chemical form is performed by plants with almost 100 per cent efficiency; transmission of information within the nervous system is more complex than the largest telephone exchange; problem solving by a brain exceeds by far the capacity of the most powerful computers; blind bats' location of their prey by supersonic vibrations is a precursor of submarine hunting by sonar (see Fig. 1); the selectivity of frog's eyes has inspired the design of an electronic system that can discriminate between 'meaningful' and 'meaningless' flying targets and report, for instance, only those aircraft and missiles that are potentially dangerous; and so on. The field of action open to mimicry of nature is limitless.

One aspect of the study of living beings that is likely to provide new clues to make new machines and systems is the chemistry of nature. It is far subtler and defter than any we have yet invented. Consider, for instance, the

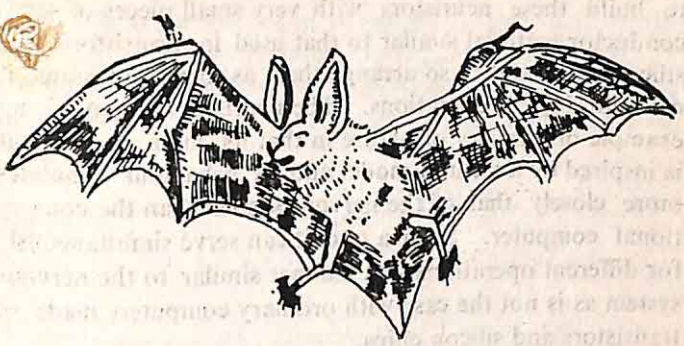


Fig. 1 : The bat uses a 'sonar' system to fly with great accuracy, without colliding against walls or other obstacles even in total darkness, even though its eyes are very poorly developed. The bat, while flying, produces a series of shrill cries which are inaudible to the human ear. These are reflected back as echoes from nearby objects. The bat is able to avoid collisions by noting these echoes.

working of neuron, the basic fabric of our own brain. Unlike its man-made counterpart, the transistor, or even its more miniature version, the silicon chip, the prime component of the computer, it is both digital as well as hormonal. Even more remarkable, the neural impulse it transmits travels in only one direction from the sense organs along its axon and without weakening in transit.

This property makes the nerve axon a very special kind of cable capable of logic operations but very different from man-made conductors such as long-distance telephone wires, wherein the signal is attenuated during its propagation requiring boosters on the way to amplify it. Although our understanding of the way neurons function is still very rudimentary, it has already led to a new device called a neuristor. It mimics the neuron in that it permits one-way propagation of a signal without attenuation. It is possible

to build these neuristors with very small pieces of semiconductor material similar to that used in transistors and silicon chips and to so arrange them as to perform numerical and logical operations. The neuristor computer is an example of mimicry of nature in that its main component is inspired by a natural model and its behaviour simulates more closely that of the nervous system than the conventional computer. Such a circuit can serve simultaneously for different operations in a manner similar to the nervous system as is not the case with ordinary computers made of transistors and silicon chips.

Biochemical insights are also suggesting ways of duplicating the extremely refined sensory mechanisms of animals and plants. To illustrate, the layer method, whereby chlorophyll in plants captures sunlight for their sustenance, underlies the design of recently developed solar batteries. Only nature has anticipated our inventiveness by a billion years or more. Likewise, skills and sensitiveness of rattle snakes and tropical fish, not to speak of our own brain, are now known to be far superior to any apparatus that we can yet make. Thus, rattle snakes carry a heat-detecting device which enables them to locate their distant prey by responding to a temperature change of one thousandth of a degree. Similarly, a certain tropical fish can detect miniscule currents of one hundred billionth (10^{-11}) of an ampere per square centimeter on its body. Such a delicate sensitivity permits the fish to discriminate between glass rods that differ in diameter by less than one-tenth of an inch. But the most spectacular is the performance of the neurons of our own brain, whose compactness and economy of performance no semiconducting transistor, silicon chip or even neuristor, has yet been able to match. When we begin to understand the chemical basis of these sensitivities and skills more fully than we do at present, we shall be able to

add wings to chemistry and engineering. One may, therefore, say of nature's chemistry what Hamlet said of Horatio's philosophy : there are more things in the world of chemistry than any yet dreamt of by the chemists of today!

21 *On Spurring Nature*

One of the most urgent problems facing scientists today is how to spur nature, that is, hasten the occurrence of certain natural processes that sustain human life. One such natural process is photosynthesis whereby green plants capture sunlight and store it as chemical energy in organic productions, particularly carbohydrates. In the past, green plants growing in warm climates, increased in numbers faster than they were consumed. As a result, abundant supplies of fossil fuels (coal, oil and gas) were deposited in the earth's crust. At the rate we are consuming them now they are likely to be exhausted in the next 50 to 200 years or so.

Growing more forests for fuel means less land for food in a world where the human population is increasing exponentially. An obvious way out of this food versus fuel dilemma is to examine whether we can accelerate sufficiently natural photosynthesis to produce both food and fuel for the rapidly proliferating population of our world. Some recent studies have encouraged the hope that it might be possible to do so.

Natural photosynthesis (Fig. 1) in plants occurs in two stages—a photochemical or light-dependent stage, and an enzymatic, or dark stage that involves chemical reactions. The first stage is known as the light reaction, wherein

chlorophyll, the stuff that gives plants their green pigment, captures rays or photons of sunlight to split water into oxygen, protons and electrons.

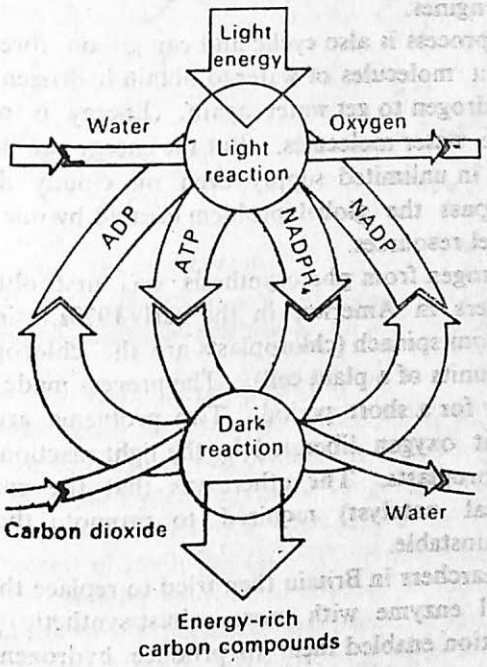


Fig. 1 : The mechanism of photosynthesis.

The second stage, which does not require light, is called the dark reaction. This uses the electrons generated in the first stage to convert atmospheric carbon dioxide into carbohydrates. What scientists are trying to do now is to spur natural photosynthesis by omitting the dark reaction.

They hope to do so by diverting the electrons to convert protons into hydrogen. After all, a hydrogen atom is only in proton with an electron spinning round it. If hydrogen

is produced by the proposed variant of natural photosynthesis, the prize is a virtually limitless supply of renewable energy. Clean and easy to store, hydrogen can be burned as a fuel in suitably redesigned aircraft and automobile engines.

The process is also cyclic and can go on forever. We first split molecules of water to obtain hydrogen and then burn hydrogen to get water again. Energy is needed to split the water molecules. But the energy can be sunlight which is in unlimited supply even on cloudy days. We thus bypass the global problem created by our depleting fossil fuel resources.

Hydrogen from photosynthesis was first obtained by researchers in America, in the early 1970s, using chloroplasts from spinach (chloroplasts are the chlorophyll-containing units of a plant cell). The process made hydrogen but only for a short period. Two problems arose. One was that oxygen liberated by the light reaction poisoned the chloroplasts. The other was that the enzyme (or biological catalyst) required to promote the reaction proved unstable.

Researchers in Britain then tried to replace the unstable bacterial enzyme with more robust synthetic ones. The substitution enabled them to produce hydrogen continuously for up to six hours. But the process was still too slow to be commercially viable.

The latest results from America have now shown that a synthetic cousin of chlorophyll called porphyrin is a better substance for promoting photosynthesis. Both chlorophyll and its synthetic cousin have at their centre a metallic element (magnesium in one case, zinc in the other) which is excited by photons. The element is surrounded by nitrogen atoms, which anchor the metal, and by an outer ring made mostly of carbon and hydrogen atoms, which provides a

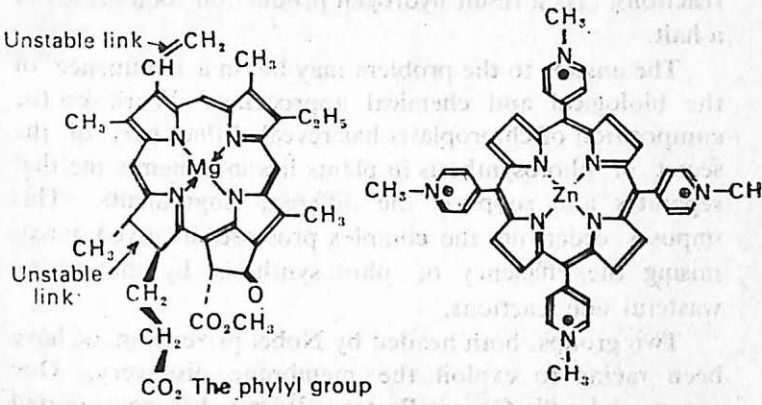


Fig. 2 : (*a*) Chlorophyll—nature's photocatalyst. (*b*) Zinc metalloporphyrin—synthetic cousin to chlorophyll.

framework for trapping photons (Fig. 2).

Over the aeons since the emergence of life on earth the structure of chlorophyll has evolved to be specially efficient at absorbing sunlight in the visible range of wavelengths, but the resulting structure is unstable if removed from its natural habitat of the living cell. By contrast the synthetic molecule is simpler and more robust. It can therefore withstand the rough treatment inevitable in a commercially viable chemical process. It is also soluble in water which is an advantage when it comes to splitting water. Essentially what happens is that a synthetic porphyrin, excited by light, releases an electron which is used to make hydrogen. Having lost an electron the porphyrin is now positively charged, which makes it attract another negatively charged electron so that the process is self-sustaining in the presence of light. It is also 90 times faster. But since the reaction occurs in a solution—in which all the ingredients tend to bump into one another—excited electrons soon begin to interact with other elements causing unwanted side

reactions. As a result hydrogen production soon grinds to a halt.

The answer to the problem may lie in a confluence of the biological and chemical approaches. Work on the composition of chloroplasts has revealed that part of the secret of photosynthesis in plants lies in a membrane that separates and supports the different ingredients. This imposes order on the complex processes involved, maximising the efficiency of photosynthesis by minimising wasteful side reactions.

Two groups, both headed by Nobel prize winners, have been racing to exploit the membrane discovery. One group, under Sir George Porter in Britain, has incorporated manganese-containing porphyrins into artificial membranes and has managed to reproduce the light reaction. The other group under Professor Melvin Calvin in California, has used zinc oxide semiconductors covered with dyes, to achieve similar results. But as yet neither reaction can be sustained for long ; both the porphyrins and the dyes break down easily.

Although complete success has so far eluded both groups it seems that their subtle and defter approach to harness solar energy has greater chance of an ultimate win, than the brute force methods also in the run such as concentration of sunlight by giant mirrors or its storage in equally gargantuan solar batteries.

Food for the Famished 22

United Nations estimates of 1977 gave the number of famished people in the world living at the survival threshold as roughly one billion. Since the world population is currently increasing by two per cent annually, while agricultural production grows at less than one per cent, the number of famished people is likely to double by the year 2000, now a mere 800 weeks away. Moreover, the demographic momentum that is expected to carry the global population to over six billion by then will be far from exhausted. It will not peter out and thereby secure zero growth before the concluding decades of the *next* century. In the meantime world population is likely to rise to eleven billion—nearly three times the present number—before it is stabilized. These projections would seem to confirm the view of those whom the popular press calls ecologists, that mankind is doomed to perish from starvation before long.

In a recent book, *Food For the Future*, Prof. Keith Campbell debunks the view of these doomsday men. He bases his case on the suggestion made by many agricultural scientists that even without fundamental advances in farm practice vastly greater productivity is possible in many parts of the world. A case in point is the striking report published in 1976 by P. Bursigh, H.D.J. Van Heemst and

G.J. Staring of the Agricultural University, Wageningen in the Netherlands. It shows how the world's cereal production may be increased forty-fold!

The Wageningen estimate of increased potential of global cereal production may seem incredible. But there is no doubt that if only certain constraints on cereal production (to which I will revert later) were overcome, world cereal production would increase at least five to ten-fold in the next hundred years. Even if we manage to secure only a five-fold increase, it will be possible to feed any increase in population before it is contained at a satisfactory level (as far as food production is concerned). Since the most likely estimate at which the world population will stabilize itself is around eleven billion, there is reason to hope that they can all be fed. This is not to deny the Malthusian view that if the world population *continues* to increase at the present rate there must eventually be more people than can be fed. The prospect of adequate cereal production in the next century is, therefore, no reason why we should not curb our population explosion right now.

If world cereal production can be raised to feed the famished millions of the Third World, why is it not raised? Paradoxically the reason is not the obvious limits to crop growth such as lack of arable land and shortage of water. These indubitable limits can be transcended to a great extent by resort to scientific agriculture. It is now being increasingly realized that intensification of scientific agriculture that brought in its wake what is called Green Revolution can boost agricultural productivity way beyond what has already been reached. The new levels of productivity are not being attained mainly because of two constraints. First there are scientific and agricultural problems—how much food can we produce; will there be

land, water, energy and other resources; can the land sustain the present pressure? Secondly, we have economic and political problems—will farmers make a decent living; or will economic and social pressures make them work below their maximum productivity level. The first set of problems are soluble if agricultural research is better organized. The main hurdle is the existing isolation of research workers from farmers resulting in the usual proliferation of unproductive bureaucrats, particularly in the least productive countries such as India and Bangladesh. More serious is the constraint of economic and political policies which encourage low productivity mainly in the richer countries. Price control, quotas and other measures adopted by governments to influence agriculture have been severely and convincingly criticised by many economists and agricultural experts. (Prof Campbell is only a recent addition to their number.) The nub of their criticism is that poverty rather than low food production is the main cause of hunger in the world today. We ourselves have been carrying in the past few years a huge surplus of grain not because there were no hungry people to eat it but because they were too poor to buy it. The phenomenon is global.

If the poor had more money to buy the food they need, the 'surplus' grain of the affluent nations would vanish instantly. Increased consumption would stimulate further production as increased food production could be made profitable to the producer. It therefore seems that world food production, if freed from existing trammels, would be sufficient even today to give the present population a nutritionally adequate, though dull, largely meatless diet. The famished one billion of today could then be given the minimum calories they need though it will mean less grain for the production of luxury food the richer nations now consume.

A spectacular demonstration of the way foodgrains are diverted from feeding the hungry to luxury food for the well-fed occurred in 1973. World wheat prices shot up because Russia had the money to buy a larger than usual share of the world surplus, thus pricing the poor countries out of the market. This grain was bought to feed pigs which had more economic power than the starving millions of the Third World. If the Soviet pigs showed their economic teeth only once in 1973, European and US pigs have been grinding them, albeit invisibly, all the while as they still continue to do. They are consuming much of the world's surplus grain to produce luxury food for their rich domesticators.

Since the rich will not reorganize their feeding habits merely to feed the hungry, the famished of the world can look forward to substantially better diets in the future only if the potential cereal production is actualized by doing away with current curbs on cereal production.

When Chance Becomes Necessity 23

If there is a small chance—say, one per cent—of your losing a game, it is reasonable to assume that you will lose once in 100, twice in 200, thrice in 300... plays of the game. There is, however, one game—the birth control game—where a small chance of a failure is no better than a big one. It is like a long voyage in a ship without pumps and without any means of repair on board. Its ultimate destination is the same—the bottom of the sea—if the ship springs a leak no matter what the size of the crack, whether a small crevice or a big hole. Let me explain the similitude.

Suppose you have three different types of contraceptives *A*, *B*, *C*, with respectively, 1, 10 and 50 per cent chance of failure. If you use consistently any one of these devices (such as *A*) throughout your reproductive life of some 40 odd years, the number of failures may not be the same as when you use *B* or *C*. But, paradoxical as it may seem, the number of resultant pregnancies will remain practically the same irrespective of the contraceptive used! For, after all, even when a couple does not practise birth-control, the wife does not incur infinite pregnancies.

Ordinarily, only eight to ten pregnancies, on an average, materialize in a lifetime. Biological constraints of human procreation ensure that all contraceptive devices

with almost any positive (non-zero) chance of failure are on par in so far as their ultimate practical outcome is concerned. They are like the ship mentioned earlier in their ultimate upshot.

The ultimate efficacy of a contraceptive is then like the seaworthiness of a ship or the virginity of a girl. It is not a continuous function capable of taking all values between 0 and 1—or between 0 and 100, if you reckon in percentages. It is a two-step function—either 0 or 1. It has, therefore, as little to do with the failure frequency of the contraceptive used, as seaworthiness has with the size of the leak or virginity loss with the weight of the baby born. There is no merit in the legendary virigin's expiation of her sin on the plea that the baby she gave birth to was such a tiny creature!

Since the ultimate efficacy of a contraceptive, having regard to the overall biological situation under review, is either total or nil, what is the use of an oral pill, vaccine, condom or loop with a failure rate of 1 per cent instead of 10 or even one-tenth per cent instead of one?

Yet despite the virtual parity of all contraceptive devices with almost any positive (non-zero) failure frequency, laboratories and institutes are busy researching how to further reduce the failure rate of their favourite device. It is seldom appreciated that what is relevant here is not diminution but extinction. For lack of such appreciation, sham research continues quite oblivous of the fact that, even if successful in achieving the desired goal (which I doubt), it will only be a futile duplication. Futile because it is not a once-for-all-time operation. Being a repetitive act, it will not always be performed in the regulation way. Murphy's law will then see to it that, if anything has a chance to go wrong, it certainly will. Chance then becomes necessity. Duplication because we already have in one-

step vasectomy, a means with zero failure frequency.

Now, if further research in the improvement of contraceptive techniques is no longer worthwhile, what then must we do to control our exploding population?

Population control depends on two components: incentive and technique. It is curious that ancient societies with enormous incentive but poor technique managed to control their population whether by abortion, infanticide, human sacrifice, religious celibacy, Malthusian checks or what-have-you. Modern societies, on the other hand, with perfect technique (vasectomy) but poor incentive, have failed. The reason is that ancient societies, innocent of contemporary science and technology, were far more aware of the limits of their environments even if this awareness was the outcome of mere gut feeling rather than conscious reflection. We, on the other hand, think ourselves too clever. We seem to imagine that our science and technology can rescue us from all predicaments of our own making by appropriate 'technological fixes'. As a result we have no incentive to employ the perfect technique we already have.

Since the technique exists but the incentive is lacking, is it not obvious that research priority should be motivation, not technique? There are many reasons why most people are averse to vasectomy. Some have a horror of any surgical operation, no matter how trivial, and will not undergo it, except under some stern duress, such as serious sickness or unrelieved agonizing pain. Others think it is an unwarranted interference with the normal working of the healthy body. But the vast majority of our people, particularly those living in the villages, abhor vasectomy since they look upon it as virtual castration. They do so because this is precisely what a peasant does when he no longer wants his bull to reproduce.

How to remove this misapprehension is thus the basic question we can no longer evade. It seems to me that the credibility gap here is too great to be bridged by mere preaching. What is required is an ocular demonstration of the behaviour of two groups of bulls, one castrated and the other sterilised, in a herd of cows. Seeing is believing!

On Scaling Up 24

Dr. Johnson is said to have belitttled *Gulliver's Travels* on the rather flimsy ground that once you have thought of scaling up (or down) a normal human being about twelve-fold, the rest follows automatically. His criticism might have been more cogent had he pointed out Swift's inadequate awareness of all the subtleties of the scaling operation he resorted to in writing his book. Swift was no doubt aware that the volume (or weight) of a scaled-up being increases as the cube of its linear amplification. Thus in Lilliput, 'His Majesty's Ministers finding that Gulliver's stature exceeded theirs in the proportion of twelve to one concluded from the similarity of their bodies that his must contain at least 1728 (or 12^3) of theirs, and must needs be rationed accordingly'. But he did not realise that the same principle of scale applied to the brobdignagians would make their existence impossible, even though Galleo Galilie had demonstrated such impossibility a century before him. In a famous passage Galileo had written:

> ...it would be impossible to build up the bony structures of men, horses or other animals so as to hold together and perform their normal functions if these animals were to be increased enormously in height, for this increase is accomplished only by

employing a material which is harder and stronger than usual, or by enlarging the size of the bones, thus changing their shape until the form and appearance of the animals suggest a monstrosity.

This is perhaps what our wise poet had in mind, when he says, in describing a huge giant:

Impossible it is to reckon his height
So beyond measure is his size.

And yet Swift dared to create his brobdignagian giants by envisaging scaled-up beings twelve times taller than Gulliver. But in scaling them up Swift ignored other important factors that such scaling up brings into play. Since the brobdignagian is twelve times as high as Gulliver his total volume (or mass) will be about 1728 (or 12^3) times as great. But as the cross sections (or areas) of his bones are only 144 (or 12^2) times those of Gulliver's, every square inch of the giant's bone has to support $1728/144 = 12$ times the weight borne by a square inch of Gulliver's. As the human thigh-bone breaks under about ten times the human weight, a brobdignagian would have broken his thigh every time he took a step. By the same token it is doubtful if he could even sit, let alone stand up as the hip bone, which has to endure the weight of his trunk, would have been no stronger that that of his thigh. This is also why it was no great feat, as the legend has it, that David felled Goliath with a sling shot. The poor giant would have collapsed under his own weight the moment he stood up to engage in the fight!

But if gravity is a major obstacle to the making of a brobdignagian, it is not even a minor nuisance to a lilliputian. The reason is the same as before but now acting in reverse. A twelvefold miniaturization will *increase* twelvefold the lilliputian's surface vis-a-vis its volume, exactly as a similar amplification *decreases* it.

Now the air resistance presented to the fall of a body under gravity is proportional to its surface area (which is why a feather falls more slowly than a tiny ball-bearing of the same or even smaller weight). Accordingly the resistance to falling in the case of the small lilliputian is twelve times greater than the driving force. A lilliputian can therefore fall without much danger.

But the same increase in the relative size of its surface area makes another force of nature as formidable to him as gravity is to us. This force is surface tension, the force that exists in any boundary surface of a liquid such as water. A man coming out of a bath experiences negligible surface tension. But a wet lilliputian, if he were as small as a fly, would be in a very perilous situation indeed. If he went out for a drink, he would be in as great a danger as a man on a tall tree-top plucking a coconut to eat. One is as likely to fall in the grip of surface tension of water as the other in that of earth's gravity. For if the former were to come too close to water as to get wet, the surface tension of water is likely to hold him there until he drowns.

However, there is yet another still more fundamental snag to a lilliputian's very existence than surface tension. It is this. While scaling down might preserve the similarity of the external geometrical forms of the human and lilliputian bodies, it cannot preserve that of their internal organs such as the brain and the eyes. A lilliputian will have no room to house a brain of any comparable, let alone similar, intelligence or even eyes of sufficient acuity to observe a Gulliver. In other words, a scaled-down version of man, the lilliputian, cannot exist any more than a scaled-up brobdignagian. Both scaling operations (up and down) lead to blind alleys of their own.

But it is easy to be wise with hindsight. If Swift was

unaware of the finer nuances of the scaling operations despite Galileo, so were, with far less justification than him, almost all the students of zoology and animal forms till our own day! For the grand theme of scaling—that the effect of scale depends not on the thing in itself but in relation to its whole environment or milieu was not broached till the appearance in 1917 of D' Arcy Thompson's great book, *On Growth and Form*. He it was who first convincingly showed that for every type of animal there is a most convenient size, and a large scaling up or down inevitably carries with it a change of form. It no longer remains the same being.

D'Arcy Thompson begins his book with an eloquent invocation to mathematics though the mathematics he applauds has a curious ring. We find none of the differential equations, mathematical statistics and other heavy armour of modern mathematics that geneticists, demographers, ecologists and biologists nowadays employ. He has recourse to much simpler notions such as partitioning of space, the Meraldi angle, the logarithmic spiral and the golden mean. Numbers rarely enter his equations, rather they exemplify geometry. For D'Arcy Thompson was a Greek mathematician with 20th century material and insights. He used these assets to demonstrate that organic shapes conform to the physical forces—such as gravity, surface tension or even Brownian motion in the case of microscopic beings such as bacteria—prevailing at their scale. He showed that the pervasive effect of size upon form is a simple consequence of physical laws and geometric arguments. He thus turned the study of form into a science which explains some of the most puzzling and paradoxical facts of life: why any fly can walk up a wall; why elephants have thicker legs than gazelles; why eagles are not as large as tigers; why the giant ants of

Them really couldn't have reached the Los Angeles sewers; why size for size an elephant is much the *weaker* vessel than an ant; and so on. You will find the answers to these and similar questions in D'Arcy Thompon's charming book. In answering them he shows that if God had any hand in the matter, he had worked in a rather mundane fashion through the physical laws of size and scale!

A Century of Darwinism 25

As is well known, Charles Darwin was the first to show in a convincing manner that animals and plants living today had not arisen by special creation of each species but by slow descent from very different ones in the past, some of which have left fossils. But despite a most thorough and objective analysis of the data from all fields of biology to prove organic evolution through natural selection of variations that were in their origin non-adaptive, his theory remained essentially negative. While it did account for the extinction of some forms and persistence of others by the 'survival of the fittest', it could throw no light on the 'arrival of the fittest' in the first place. It could not possibly do so because the mechanism of heredity had yet to be discovered.

In the absence of an adequate theory of genetics, Darwin could give no satisfactory account of the variations on which natural selection would later act. Although the laws governing the mechanism of heredity were discovered by Gregor Mendel at about the same time as Darwin formulated his theory of evolution, Mendel's discovery remained unnoticed by his contemporaries including Darwin. He actually possessed a copy of Mendel's monograph on heredity which he hadn't bothered to read.

It was only around the turn of the century that laws of

heredity began to be rediscovered and became the basis of the chromosome theory of genetics now in vogue. The first impact of the rediscovery of Mendel's law was curiously odd. It turned the early Mendelians into anti-Darwinians. They saw 'mutations'—spontaneous gene changes—which they studied as the only source of heritable variation. Each mutation alone could, therefore, be the starting point of a new species. Accordingly such species could only emerge readymade without previous selection very like Athena springing out of Zeus' head and *not* by the gradual accumulation of slight changes that Darwin's theory required.

Darwin's banner was held aloft by their anti-Mendelian rivals of the biometric school. They concentrated on measuring the correlations between relatives and looked upon genes suspiciously as metaphysical entities of dubious relevance to biological evolution. Indeed, they regarded mutants as pathological deviants doomed to early elimination by natural selection, and continous variation as the sole spur to evolution. The argument led by Bateson, on the side of Mendelians, and Karl Pearson, on that of the Biometricians, foreshadowed the current debate between 'punctualists' and 'gradualists' of which more later. It is a part of the larger debate between those who view the world as a continuous progression of gradual changes and those who think it is a sequence of discrete leaps or 'quantum jumps'.

The debate, at least in the form in which it then presented itself, was largely settled by the work of population geneticists R.A. Fisher, J.B.S. Haldane and S. Wright. They did so by showing that the system of Mendelian genes that mutate occasionally, segregate and recombine at random, provides exactly the mechanism required to e xplain evolution by natural selection. By applying it to

the population of any given species they obtained deterministic, albeit statistical, patterns of change in the genetic representations of its succeeding generations. They could thus even test their theory by deriving conclusions which could be confronted with observational data.

The work of the population geneticists, in turn paved the way for the 'modern synthesis' of evolutionary biology developed in the period 1930-53 by a group of biologists consisting of Dobzhansky, Ford, Julian Huxley, Mayr, Muller, and others. If one were to describe in a single sentence what they did, it is this. They showed, in effect, that 'neo-Darwinian' mechanism—natural selection in Mendelian populations—was sufficient to explain the evolutionary process as it could be observed in nature. Most research in evolutionary biology since then has been carried out in the framework of the 'modern synthesis'. But now a wind of change has begun to blow in the wake of new findings of a wide diversity of disciplines such as molecular biology, developmental biology, systematics, palaeontology and the like. They have had an unsettling influence on the neo-Darwinian theory of evolution.

Molecular biologists and developmental biologists, systematists and palaeontologists have accumulated a volume of data that has a bearing on evolution. This is natural because whatever else it might be, evolution involves the modification of DNA sequences, developmental patterns and species, and higher taxa. The evolutionarily inclined practitioners of these diverse disciplines now claim that their data—their DNA molecules and fossils—have something very direct to say about the validity of this or that notion about how life really evolved. They refuse to be relegated to the role of mere reporters as hitherto and leave it to the population geneticists to explain biological evolution. Some of them have even suggested the replace-

ment of the Darwinian concept of *gradual* change within individual species population over time by the new model of evolution by sudden leaps interrupted by prolonged periods of stasis called 'punctuation'. They even acclaim their new model, the 'punctuated' theory of evolution as a full-fledged scientific revolution, even a Kuhnian paradigm.

The 'punctuated' theory views evolution as a stop-go affair with long stops punctuated by relatively brief bursts of goes. It was first proposed with particular clarity by Eldredge and Gould in a seminal paper published in 1972. According to them, most evolutionary changes occur *abruptly* when a new species develops, that is, during a 'speciation event', and none or very little subsequent to the establishment of a species. It has recently been confirmed by P.G. Williamson's presentation in October 1981 of an extraordinarily 'complete page in the history of evolution'. The 'page' is a very detailed sequence of fossil molluscs from the eastern Turkana basin in East Africa. All of the thirteen linkages, including ten which could be followed for 4.5 million years, showed a pattern of evolution conforming to the new 'punctuated equilibrium' model. Change was shown to be concentrated in short (5,000 to 50,000 years) speciation events, between long periods (3.5 million years) of morphological stasis. While such a pattern of change can be brought about by conventional Darwinian selection, it is difficult to explain why such selection remains dormant for the very long periods of stasis.

Williamson favours the view originally put forward by Eldredge and Gould that stasis is primarily the result of 'developmental constraint' which makes certain kinds of developmental change difficult or even impossible. Their reason is that the genotype (genetic constitution of any well-defined group of organisms), as a whole, is a finely

balanced system, in which appropriate feedback mechanisms maintain morphological stability by compensating for whatever genetic changes occur through time at individual loci. Consequently, stasis is what one should normally expect. A 'spectation event', that is, the irruption of a new species involving dismantling of these feedback mechanisms must necessarily occur in a sudden burst not unlike quantum jump of an electron from one atomic shell to another. Williamson sees evidence of this process in the periods of extreme developmental instability (recorded as an increase in phenotypic variance) that accompany speciation events in his mollusc sequences.

The 'punctuated' theory of evolution is, no doubt, based on recent paleontological studies. Numerous fossil species have been found which exhibit a remarkable degree of stability of 'morphological stasis, over long periods of geological time. But it has not yet been able to counter successfully two main objections.

First, fossil record on which it is based can only be obtained for certain body parts—molar teeth of mammals or shells of molluscs, for example. So, it is paralogical to conclude that entire organisms remain unchanged over time. Differential evolution of individual body components (mosaic evolution) is a widely recognised phenomenon, and there is, for instance, no indication of stasis at the level of structural gene. Moreover, recent work on molecular evolution strongly suggests a haitus between rates of evolution of single proteins and those of whole organisms. It is, therefore, all too easy to slip into equating fossilized skeletal parts with entire organisms. Many biologists are of the view that this slip runs through the literature of 'punctuated' evolution as a recurrent refrain.

Secondly, rapid evolution during speciation is inferred from the fossil record on the tacit assumption that it is

sufficiently complete to document the process unequivocally. Unfortunately, the fossil record as a whole is pitifully inadequate. There is, for example, one major fossil site recording the occurrence of mammals in the entire African continent for the first 35 million years of the Tertiary. We really need to have estimates of the relationship between the likely catchment areas of relevant fossil sites and the geographical ranges of equivalent modern species. In the absence of such estimates a reasonable guess is that fossil sampling is in fact extremely patchy. This is why the 'punctuated' pattern of evolutionary change seen in Williamson's and other findings has been viewed in some quarters as an 'artifact of the sampling time scale'. The argument has recourse to a thought experiment designed to show that too fine or too coarse a time scale on which fossil observations are made will always lead to a more gradual picture, whereas at some intermediate scale the process will appear as 'punctuated'.

Nevertheless, the picture now emerging from the fossil record is unsettling, and our ideas of evolutionary process must undoubtedly progress to account for long-term stasis, at least in individual body parts, in species population. The question is whether such progress requires a minor modification of the 'neo-Darwinism' of population geneticists hitherto in vogue, or whether the changes which occur during speciation dictate the recognition of a radically new paradigm like the 'punctuated' theory of evolution. There is as yet no unequivocal answer to the question.

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